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**An exploration of the outcomes and experiences of people
living with cognitive impairment and intracerebral
haemorrhage: a mixed methods approach**

Katie Louise McGoohan

Thesis presented in fulfilment of the requirements of the degree of Doctor of
Philosophy in Nursing Studies

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Abstract

Introduction

Stroke due to intracerebral haemorrhage (ICH) is the most devastating and least treatable type of stroke, where onset is sudden, often leaving the individual and family ill-prepared to deal with the long-term consequences. Associations between cognitive impairment and ischaemic stroke have been well described in the literature however fewer data are available for ICH and cognitive impairment. Although some studies have investigated the prevalence and risk factors of cognitive decline before and after ICH, very little is known about the influence of cognitive decline on functional outcome after ICH. Furthermore, there have been no qualitative studies designed specifically to examine the experiences of people living with cognitive impairment after intracerebral haemorrhage.

Aims

To explore the outcomes and experiences of people living with cognitive impairment and intracerebral haemorrhage:

- (a) To study the prevalence of pre-existing dementia and cognitive impairment in patients with ICH, and to quantify their incidence at specific time points thereafter,
- (b) To investigate the demographic, clinical, radiographic and functional outcomes associated with the occurrence of cognitive impairment following an ICH, and
- (c) Evaluate the experience of life after ICH with cognitive impairment.

Methods

(a) A retrospective analysis of all patients diagnosed with ICH in one region of Scotland between June 2010 and May 2013, who had available CT data from the time of the index ICH (n=404), was conducted. Data were taken from the Lothian Audit of the Treatment of Cerebral Haemorrhage, including people aged ≥ 16 years at the time of diagnosis. Data on demographics, medical history, and medication was drawn on. In addition to determining the

prevalence and risk factors of pre-existing cognitive decline, survival analysis was used to determine cumulative rates of patients remaining free of cognitive decline up to 5 years after their ICH (LATCH COG).

(b) A prospective observational cohort sub-study (LINCHPIN COG) of adults with ICH (n=45) was conducted using a detailed assessment of cognition and functional outcomes at 6 and 12-24 months after ICH. Pre-existing cognitive decline was measured using the IQCODE informant questionnaire, whilst also collecting basic demographic data, data on vascular risk factors, stroke severity, level of dependency, and neuroimaging features on computed tomography and magnetic resonance imaging. The primary outcome was new-onset cognitive impairment (defined as MoCA score <26) at 6 months, when functional outcomes (depression, fatigue, health-related quality of life) were also measured.

(c) In an embedded qualitative study, six ICH survivors and four family members participated in semi-structured interviews and gave details about their experiences of life after ICH. The data collected was analysed using a thematic analysis approach.

Results

(a) Using data from LATCH COG, I found that roughly 1 in 4 (23%) patients had cognitive decline prior to their ICH. Forty-one patients (10%) had cognitive impairment with no dementia. Fifty-two patients met the criteria for pre-existing dementia (13%).

In univariate analysis of LATCH COG, CT neuroimaging markers of cerebral amyloid angiopathy and small vessel disease were associated with pre-existing cognitive decline. In logistic regression analysis, patients who had a lobar ICH were twice as likely to exhibit pre-existing cognitive decline and 3 times more likely to exhibit pre-existing dementia than those who had a non-lobar ICH. Patients with central (deep) atrophy were over 4 times more likely to exhibit cognitive decline and 8 times more likely to exhibit dementia before their stroke than those without. In line with this, severity of white matter changes was associated with pre-existing cognitive decline, suggesting a neurodegenerative process. Increasing age and larger haemorrhage volume were also associated with an increased likelihood of patients having cognitive decline prior to their stroke.

During the first 5 years of follow-up of LATCH COG, of the 168 patients who survived longer than 30-days after their ICH, 47 patients developed new-onset cognitive decline (cognitive impairment and dementia). Cumulative survival rates for patients remaining free of cognitive decline were 82% in the first year and 65% at 5 years.

In univariate analysis of LATCH COG, presence of posterior white matter lucencies was associated with new-onset dementia, indicating an association with markers of small vessel disease. In Cox regression analysis, patients who had a lobar ICH were twice as likely to exhibit new-onset cognitive decline than those who had a non-lobar ICH. In those who survived past 30 days, the incidence of new-onset cognitive decline was 37% in patients with lobar ICH and 20% in patients with non-lobar ICH.

(b) Cognitive impairment is frequent after ICH with 43% of participants from LINCHPIN COG scoring <26 on the MOCA at 6 months.

In univariate analysis of LINCHPIN COG, new-onset cognitive impairment at 6 months was associated with pre-ICH history of hypertension. I could not detect statistically significant associations between new-onset cognitive impairment and functional outcomes at 6 months. The small sample size may have been a significant contributory factor, making it difficult to identify any statistically significant differences between those with and without cognitive impairment

(c) Thematic analysis of the qualitative interviews identified four overarching themes relating to how survivor's and their family members experienced life after stroke: 'the effects of stroke on sense of self and identity', 'adaptions and adjustment', 'uncertainty', and 'impact on family members'. These findings were interpreted in relation to theories of biographical disruption and suggest the necessity for individualised assessment of needs and the planning of services to best assist stroke survivors in coming to terms with their illness and its long-term consequences.

Conclusion

Pre-existing cognitive decline affects more than one-fifth of patients with ICH. For survivors of ICH without pre-existing cognitive decline, over two-fifths develop new-onset cognitive impairment by 6 months after ICH. Neuroimaging markers of cerebral amyloid angiopathy

and small vessel disease were associated with pre-existing and new-onset cognitive decline. New-onset cognitive impairment at 6 months was associated with pre-ICH history of hypertension. This implies an important role of vascular processes on the pathophysiology of post-ICH cognitive decline. The qualitative accounts in this study indicate the devastating effect that a stroke due to haemorrhage can have on the lives of survivors and their families, with participants often indicating that they could no longer be the person that they were before the stroke. These data may help inform patients, their family and caregivers about the risk of cognitive impairment after ICH and its resultant impact on the lives of survivors.

Lay Summary

Imagine waking up one day and not being able to find the words to talk to your family or friends? For many, this is the reality of life after stroke. Each year, around 150,000 people in the UK have a stroke, which is roughly one stroke every five minutes.

A stroke is a brain attack. It happens when the blood supply to part of the brain is cut off, killing brain cells. There are two main types of stroke: ischaemic and haemorrhagic. Ischaemic stroke occurs when a clot is formed and blocks off blood supply to part of the brain. Stroke due to bleeding in the brain, also known as a haemorrhage, is the most devastating and least treatable form of stroke. Within one month of the haemorrhage over 40% of patients will have died. More than half of the people who survive a brain haemorrhage are left dependent on family members or carers as a result of the long-term consequences.

One such consequence might be problems with thinking, known as cognitive impairment. Cognitive impairment is an umbrella term for a range of symptoms, including memory loss, problems with thinking, and difficulties in speaking, understanding, reading and writing. Cognitive impairment can make simple tasks, such as making a cup of tea, very difficult and may worsen over time, leading to a diagnosis of dementia. Stroke and cognitive impairment are closely related. However, most research in this area has focussed on patients who had an ischaemic stroke.

This is where my PhD comes in. Survivors of stroke due to haemorrhage were given the opportunity to take part in a detailed assessment of their cognition at 6 and 12-24 months after their stroke. In addition to simply looking at the number of stroke survivors with cognitive impairment, participants were also offered the chance to have an MRI scan of their brain so that I could look for potential risk factors, for example the location of the bleed and how that affects cognitive impairment.

I found that around 1 in 4 (23%) patients had cognitive impairment before their stroke, and over two fifths (43%) developed new cognitive impairments 6 months after their stroke.

In this study, cognitive impairment seemed to be a consequence of small vessel disease, which is caused by the narrowing of small blood vessels deep inside the brain. I also found that cognitive impairment was strongly linked to having a history of high blood pressure.

Although my findings would support the reduction of cognitive impairment using blood pressure lowering tablets, at the moment, relatively little is known about the link between high blood pressure, its treatment and cognition impairment.

However, this is not the full story. We know very little about what having a cognitive impairment means to stroke survivors. As such, I decided to carry out interviews with a small group of participants to find out whether the cognitive impairments were interfering with their daily lives. What I found was that, despite many of the participants having other issues, such as problems with mobility or mood, it was often the cognitive impairment that was the biggest thing to happen to them.

No matter whether the participant wanted to be able to say their wife and children's names, learn the skills needed to drive their car, read to their grandchildren or return to paid employment, it took hard work, determination and a really good support network. However, not everyone had this. Although rehabilitation services in the community were available for most, it simply wasn't enough. Many of the stroke survivors felt abandoned after they left hospital and missed out on services that could have supported them to achieve their best possible, individual, quality of life. Patients need to feel empowered through tailored support and improved rehabilitation. Getting these basic things right could transform the lives of many people and their families.

This is why research like this is so important. By gaining a more comprehensive picture of the stroke experience through the use of both questionnaires and interviews, I am hopeful that we can use this information to improve services so that we can help more people get back to doing the things they love after stroke.

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Abbreviations

ACE-III	Addenbrooke's Cognitive Examination-III
AD	Alzheimer's disease
APOE	Apolipoprotein E
CAA	Cerebral amyloid angiopathy
CAMCOG	Cambridge Cognitive Examination
CDR	Clinical Dementia Rating
CT	Computed tomography
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
EQ-5D	EuroQOL-5D
HRQOL	Health-related quality of life
ICH	Intracerebral haemorrhage
IQCODE	Informant questionnaire of decline in the elderly
LATCH COG sub-study	Lothian Audit for the Treatment of Intracerebral Haemorrhage Cognitive sub-study
LINCHPIN COG	Lothian IntraCerebral Hemorrhage, Pathology, Imaging and Neurological Outcome Cognitive sub-study
MoCA	Montreal Cognitive Assessment
MCI	Mild cognitive impairment
MMSE	Mini-Mental state examination
MRI	Magnetic resonance imaging
NART	National Adult Reading Test
NIHSS	National Institutes of Health Stroke Scale
NINDS-AIREN	National Institute of Neurological Disorders and Stroke (NINDS)-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN)
NPB	Neuropsychological test battery
PGR	Patient Reference Group

PHQ	Patient Health Questionnaire
QOL	Quality of life
RUSH	Research to Understand Stroke due to Haemorrhage
SAH	Subarachnoid haemorrhage
SF-36	Short Form-36
SIP	Sickness Impact Profile
SIS	Stroke Impact Scale
SS-QOL	Stroke Specific-Quality of Life scale
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVD	Small vessel disease
TIA	Transient Ischaemic Attack
TICS	Telephone Interview for Cognitive Status
TMT	Trail Making Test
VaD	Vascular dementia
VCI	Vascular cognitive impairment
WHO	World Health Organization

Thesis overview

This thesis aims to explore the outcomes and experiences of people living with cognitive impairment and intracerebral haemorrhage. In the first chapter, the reader is provided with the relevant background information and is introduced to the wider context of intracerebral haemorrhage, definitions for mild cognitive impairment, dementia and vascular cognitive impairment, and the differences between quality of life and health-related quality of life. The subsequent two chapters provide in-depth literature reviews specifically looking at (1) intracerebral haemorrhage and cognitive decline and (2) the influence of cognitive impairment on health-related quality of life after stroke. Chapter 4 presents an overview of the thesis design, providing the reader with an orientation to the research studies linked to this thesis, the overall research design and ethical considerations. Subsequently, the thesis is divided into methodology and result chapters, each containing study-specific sections based upon the three research objectives. Chapter 11 presents a summary of the principal findings, drawing them together with an overall conclusion, followed by clinical implications, recommendations for future research, references and relevant appendices.

1. Background: definitions and concepts

This chapter outlines the relevant background to this thesis. It begins by setting out the current context of intracerebral haemorrhage including its incidence, risk factors, diagnosis and management. The differences between dementia, mild cognitive impairment and vascular cognitive impairment are then laid out and criteria for diagnosis provided. This chapter then ends with a brief review of the literature on definitions for quality of life and health-related quality of life.

1.1. Stroke and intracerebral haemorrhage

1.1.1. Stroke

Stroke represents a major cause of death globally and is the leading cause of long-lasting severe disability (Warlow et al, 2003; Jackman, Cumming and Miller 2016). The World Health Organization (WHO) definition of stroke is:

“rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin” (Hatano 1976 p. 541).

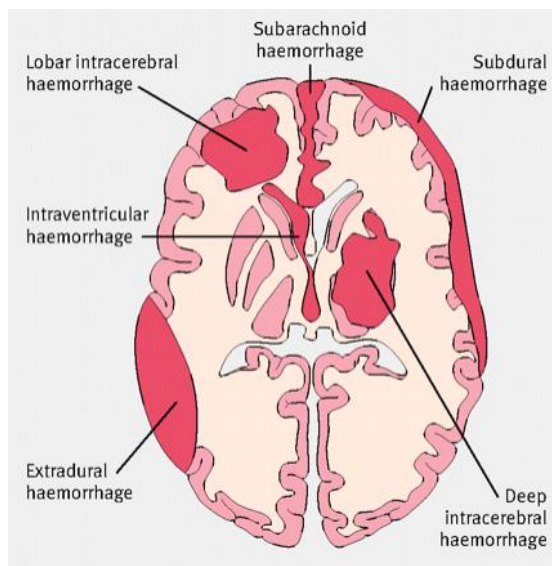
The two main categories of stroke are ischaemic and haemorrhagic.

1.1.2. Intracerebral haemorrhage

Spontaneous non-traumatic intracerebral haemorrhage (ICH) accounts for around 9-27% of all strokes (Feigin et al, 2009). It results from the rupture of blood vessels directly into the brain parenchyma, in the absence of trauma or surgery, primarily by leakages from small intracerebral arteries. The remainder of strokes are ischaemic in nature and are produced by the occlusion of a cerebral artery. ICH should be distinguished from other types of intracranial haemorrhage including subarachnoid haemorrhage (SAH), pure intraventricular haemorrhage, subdural haemorrhage and extradural haemorrhage, although an ICH may extend into one or more of these compartments (see Figure 1; Al-Shahi Salman, Labovitz and Stapf 2009). The relevance of this distinction is that the risk factors, causes and management options for each differ (Al-Shahi Salman, Labovitz and Stapf 2009).

Figure 1: Schematic diagram of the brain showing types of intracranial haemorrhage

(reproduced from Al-Shahi Salman, Labovitz, and Stapf 2009)



1.1.3. Lobar vs non-lobar haemorrhage

ICH is typically subdivided by location as being either 'lobar' or 'non-lobar', the latter of which is often referred to as deep (see Figure 1). While ICH located deep in the brain is a result of the rupture of small arterioles most commonly in the basal ganglia or thalamus, lobar ICH results from the rupture of small and medium-sized perforating arteries in the cortex (cerebrum) and subcortical white matter (Qureshi, Mendelow and Hanley 2009; Xiong et al, 2016). It is useful to discriminate between lobar and non-lobar ICH in this way because the associated causes, risk factors and likelihood of recurrence differ by location (Bailey et al, 2001; Woo et al, 2002; Samarasekera et al, 2015).

Given the distribution of vessels affected, lobar ICH in the elderly is commonly attributed to the vessel fragility and rupture caused by cerebral amyloid angiopathy (CAA) and non-lobar ICH is usually attributed to hypertension-related arteriolosclerosis (although unlike CAA, this can cause ICH anywhere in the brain) (Woo et al, 2002; Smith and Eichler 2006; Viswanathan and Greenberg 2011; Charidimou, Gang and Werring 2012). However, since any single ICH is likely to be caused by several factors, these generalisations are often too simplistic.

1.1.4. Incidence and prognosis of ICH

Stroke due to spontaneous ICH annually affects around 3.4 million adults worldwide and has a higher risk of morbidity and mortality than ischaemic strokes and subarachnoid haemorrhages (Feigin et al, 2015). The age-specific incidence of ICH is stable or decreasing, most likely due to better treatment of hypertension, which is the major modifiable risk factor. However, almost two-thirds of adults with ICH are aged 75 years or older, therefore incidence is likely to become more prevalent in our aging population (Lovelock, Molyneux and Rothwell 2007).

The recurrence rate for strokes in survivors of primary ICH is 4.3% per year (Bailey et al, 2001). From a systematic review of long-term prognosis after ICH, two studies found that the risk of recurrent ICH was higher in patients who had a lobar ICH (10%) when compared with a concurrent group of patients with non-lobar ICH (2%) (Poon, Fonville and Al-Shahi Salman 2014). Rational steps to prevent recurrence include blood pressure reduction and cessation of smoking and alcohol use (Chapman et al, 2004; Broderick et al, 2007).

Two of the greatest challenges for nursing patients with ICH are that 30-day case fatality is over 40% and over half the survivors are left dependent on family members or carers, with considerable economic consequences (Dennis 2003; Russell et al, 2006; van Asch et al, 2010). Despite advances in the treatment of cerebral infarction, there are no effective acute or specific treatments for ICH. Better prevention of ICH (first-ever and recurrent) is likely to be a more promising strategy to decrease its burden.

1.1.5. Risk factors and causes

The major risk factors for ICH are increasing age, male sex, hypertension, smoking, diet, high waist-to-hip ratio and high alcohol intake (Ariensen et al, 2003; Pantoni 2010). Many of these precipitating risk factors are likely to lead to vascular changes, such as small vessel disease, which may in turn cause ICH. Small vessel diseases are a group of pathological processes that affect the small blood vessels of the brain and are known to have ischaemic and haemorrhagic consequences (Pantoni 2010). SVD is responsible for about a fifth of all strokes worldwide and is the most common vascular cause of dementia (Wardlaw, Smith and Dichgans 2013; Wardlaw et al, 2013).

Approximately 80% of ICH is thought to be caused by SVDs, with hypertension-related small vessel disease and cerebral amyloid angiopathy (the build-up of an abnormal protein called amyloid in the blood vessels of the brain) being by far the two most common forms (Warlow et al, 2008; Pantoni 2010; Samarasekera et al, 2012). However, diagnosing these during life is currently difficult and usually made based on risk factors (e.g. hypertension and age) and neuroimaging features (Wardlaw, Smith and Dichgans 2013).

ICH has traditionally been classified as either 'primary' or 'secondary'. Primary ICH (accounting for 78-88% of cases) is attributed to the spontaneous rupture of small vessels commonly thought to be caused by chronic hypertension or CAA (Ikram, Wieberdink, and Koudstaal 2012; Smith and Venegas-Torres 2014). Secondary ICH occurs in a minority of patients and is attributable to a variety of structural abnormalities including tumours, aneurysms, arteriovenous malformations or impaired coagulation (Qureshi, Mendelow and Hanley 2009; Smith and Venegas-Torres 2014).

1.1.6. Diagnosis

The only reliable method of detecting ICH in life is early brain imaging (Al-Shahi Salman, Labovitz, and Stapf 2009). The widespread availability of computed tomography (CT) and rapid acquisition time makes it the ideal first-line diagnostic approach (Qureshi, Mendelow and Hanley 2009). CT not only defines the size, location and site of the haematoma, it also provides information about extension into the ventricular system, presence of surrounding oedema, and shifts in brain contents (Caplan 1992). Within minutes of symptom onset and up to one week thereafter, the ICH will appear hyperdense (white) in comparison to the brain parenchyma. Acute haematomas are very well defined on CT and have smooth borders. In patients who worsen abruptly, repeat CT may show enlargement of the ICH.

Magnetic resonance imaging (MRI) with gradient echo can reliably differentiate infarction from haemorrhage more than one week after stroke onset and is more accurate at detecting micro-haemorrhages (Kidwell and Wintermark 2008). MRI can also distinguish ICH from haemorrhagic transformation of an infarct using diffusion-weighted imaging and detect chronic haemorrhages (Lovelock et al, 2009). However, the use of MRI continues to be limited by both its availability and the difficulty of using it in acutely unwell patients who may have metal implants, a pacemaker, or are unable to lie flat for the scan duration (Hand et al, 2005).

In addition, a Cochrane review comparing the diagnostic accuracy of MRI and CT for acute vascular lesions concluded that while the ability of CT to distinguish acute haemorrhagic lesions from non-stroke lesions is well established, the accuracy of MRI assessment of suspected acute stroke is still somewhat unclear (Brazzelli et al, 2009).

1.1.7. Management

Guidelines recommend that patients with ICH should be managed in a stroke unit. Medical management includes intensive blood pressure lowering within six-hours of ICH onset, intermittent pneumatic compression of the legs in immobile patients with ICH, lowering intracranial pressure (if necessary), provision of hydration and nutrition, supportive care and the treatment of any medical complications i.e. seizure or infection (Broderick et al, 2007; Steiner et al, 2014; Hemphill et al, 2015). It is also recommended that subsequent blood pressure-lowering therapy is used for secondary prevention (Steiner et al, 2014).

As a stroke survivor enters into the rehabilitation phase of their recovery, efforts continue to focus on the management of physical health and incorporate additional aspects e.g. self-care, social functioning and interpersonal factors. The consequences of stroke can be far reaching and vary dramatically across different individuals. Besides reduced mobility and loss of physical functioning, research has shown stroke to impact upon individual's mental health and cause changes in cognitive functioning (Haacke et al, 2006).

1.2. Mild cognitive impairment, dementia and vascular cognitive impairment

1.2.1. Mild cognitive impairment

Cognitive impairment is not a singular concept. It incorporates multiple domains including attention (maintaining, dividing, shifting or focusing attention on a given stimulus or task, and the speed that information is processed); executive function (ability to plan, perform abstract reasoning, solve problems, focus despite distractions and shift focus when appropriate); visuospatial ability (visual search, drawing, construction); memory (ability to learn and recall new information); and language (either comprehension or expression) (

Cumming, Marshall and Lazar 2013). Because the domains are not always independent of each other, classification is often difficult- for example, remembering what items you must buy at the shops is not just reliant on memory, but also on attention and language as well (Cumming, Marshall and Lazar 2013). The accepted 'gold standard' for detecting any cognitive disturbance is a full battery of neuropsychological tests covering all domains, where normative data are used to indicate domain-specific deficits. However, this is not always feasible.

In 2011, the National Institute on Aging and Alzheimer's Association charged a workgroup with the task of revising the core clinical criteria for the diagnosis of mild cognitive impairment (MCI) (see Box 1; Albert et al, 2011 p. 272-273).

Box 1: Core clinical criteria for the diagnosis of MCI

- Concerns regarding a change in cognition
- Impairment in one or more cognitive domains
- Preservation of independence in functional abilities
- Not demented

Mild cognitive impairment is generally used to describe the symptomatic pre-dementia phase of Alzheimer's disease. The differentiation of dementia from MCI rests on the determination of whether there is significant interference in the ability to function at work or in usual daily activities. This is inherently a clinical judgment made by the clinician, based on the individual circumstances and the description of daily affairs obtained from the patient and a knowledgeable informant.

1.2.2. Dementia

Dementia is a syndrome – usually of a chronic and progressive nature – in which there is deterioration in cognitive function beyond what might be expected from normal ageing. Dementia diagnoses are most commonly based on the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria (American Psychological Association 1994). While dementia is normally characterised by a gradual decline in memory, this should also be

accompanied by disturbance in one of the following cognitive domains for a formal diagnosis to be given: language, praxis, gnosis, or executive functioning. For the DSM-IV criteria to be fulfilled, the impairment in cognitive function must be accompanied by a significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning (American Psychological Association, 1994). It should also be noted that memory impairment, although present in most people with dementia, is not an essential requirement. Rather, at least two cognitive domains must be impaired (Lopez et al, 2000). However, in addition to revising the criteria for the diagnosis of mild cognitive impairment, the National Institute on Aging and Alzheimer's Association workgroups also set out new clinical criteria for all-cause dementia (see Box 2; McKhann et al, 2011 p. 265-266).

Box 2: Core clinical criteria for all-cause dementia

Dementia can now be diagnosed when there are cognitive or behavioural symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a 'bedside' mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioural impairment involves a minimum of two of the following domains:
 - a. Impaired ability to acquire and remember new information—symptoms include repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
 - b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include poor understanding of safety risks,

inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.

- c. Impaired visuospatial abilities—symptoms include inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
- d. Impaired language functions (speaking, reading, writing)—symptoms include difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
- e. Changes in personality, behaviour, or comportment—symptoms include uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviours, socially unacceptable behaviours.

The new criteria were designed to be flexible enough to be used by both general healthcare providers without access to neuropsychological testing, advanced imaging and cerebral spinal fluid measures, as well as researchers.

Alzheimer's Disease (AD) is the most common form of dementia, accounting for up to 60-70% of cases (Ferri et al, 2005; Kalaria et al, 2008). Pathologically, it is characterised by the accumulation of amyloid beta in the brain parenchyma (amyloid plaques) or in the blood vessels (cerebral amyloid angiopathy), in addition to the presence of neurofibrillary tangles (Querfurth and LaFerla 2010). Second in prevalence is vascular dementia (VaD), which is responsible for around 20% of cases and affects more than 140,000 people in the UK each year (Gorelick et al, 2011).

1.2.3. Vascular cognitive impairment

A variety of classifications, diagnostic criteria, and descriptive syndromes are used to define cognitive impairment and dementia occurring after stroke. Vascular dementia has often been used as an umbrella term for a group of syndromes (usually relating to an abnormal executive

function that interferes with social or occupational functioning) caused by impaired blood flow to the brain and damage to the blood vessels resulting from events such as ischaemic or haemorrhagic strokes, and transient ischaemic attacks (TIA) (Khan et al, 2016).

At the severe end of the cognitive spectrum, pooled dementia rates from studies of consecutive patients hospitalised with any type of stroke indicate that about one in ten patients have dementia before their first stroke, one in ten develop new-onset dementia after their first-ever stroke, and more than one in three have dementia after a recurrent stroke (Pendlebury and Rothwell 2009). The risk for poststroke dementia is known to be highest in the first year, with an estimated incidence of 20-30%, which is nine times greater than the risk for the general population (Pendlebury and Rothwell 2009). Prevalence rates for cognitive impairment after stroke are substantially higher. In the Canadian Study of Health and Aging, 64% of stroke survivors had cognitive impairment, compared to only 21% of stroke-free controls (Jin et al, 2006).

The Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) convened an international workshop with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) to develop a research criterion for the diagnosis of VaD (Roman et al, 1993). The NINDS-AIREN clinical diagnosis criteria for *probable* vascular dementia is the most commonly cited in the literature and was recommended by the National Institute for Health and Care Guidance (NICE 2006) (see Box 3; Roman et al, 1993).

Box 3: NINDS-AIREN clinical diagnosis criteria for probable vascular dementia

- Presence of dementia- this is characterised by impairment in memory plus impairment in two or more different cognitive domains (i.e. orientation, attention, language, visuospatial functions etc). This should be established through clinical examination and neuropsychological testing. Deficits should also be severe enough to interfere with daily activities.
- Cerebrovascular Disease- defined by the presence of focal signs on neurological examination and by the presence of a relevant cerebrovascular disease on brain imaging (i.e. large vessel infarcts or extensive periventricular white matter lesions)

- A relationship between the above two disorders manifested or inferred by the presence of at least one of the following: onset of dementia within 3 months of a recognised stroke, an abrupt deterioration in cognitive functions or fluctuating, stepwise progression of cognitive deficits.

Traditionally, criteria for diagnosis of VaD are largely based on those used for AD, which does not take into consideration those cognitive deficits that are more commonly associated with cerebral vascular disease, such as attention and executive function (Jackman, Cumming and Miller 2016). In addition, the differentiation between VaD and cognitive impairment (not fulfilling criteria for dementia), is usually based on limitations in activities of daily living. In stroke survivors with substantial physical impairments, it may be difficult to assess changes in activities of daily living related specifically to cognitive problems (Ihle-Hansen et al, 2011).

Consequently, the term vascular cognitive impairment (VCI) has come to be recognised as a far more appropriate concept than VaD (O'Brien et al 2003; Bowler 2005). VCI is defined as a syndrome of cognitive impairment associated with a vascular origin (clinical stroke or subclinical cerebrovascular insult), where the cognitive impairment affects at least one cognitive domain (Hachinski and Bowler 1993). The term vascular cognitive impairment is used to encompass the full spectrum of cognitive deficits, from mild vascular cognitive impairment to vascular dementia (Gorelick et al 2011).

In 2011, the American Heart Association and American Stroke Association formed a working group that issued a consensus paper proposing a new diagnostic criterion for vascular cognitive impairment (Gorelick et al, 2011; Chertkow et al, 2013). According to the paper, VCI should include all stages of cognitive disorders associated with cerebrovascular disease, from mild symptoms to dementia. Diagnostic criteria are therefore proposed for vascular dementia (probable and possible) and for vascular MCI (probable, possible, and unstable) (see Box 4; Gorelick et al, 2011).

Box 4: Practical approach to the classification of dementia and vascular MCI

- The diagnosis of dementia must be based on cognitive testing of a minimum of four domains (executive/attention, memory, language, and visuospatial functions), and requires a decline in cognitive function from a prior baseline

in at least two domains that are of sufficient severity to interfere with the person's activities of daily living.

- Probable vascular dementia requires the examining physician to determine that the cerebrovascular disease is the dominant, if not exclusive, pathology that accounts for the cognitive deficits.
- The diagnostic criteria for possible vascular dementia are fulfilled if there is evidence of cognitive impairment and a cerebrovascular disease but there is no clear evidence of a relationship between the two (temporal, severity or cognitive pattern).
- The diagnostic criteria for probable and possible vascular MCI parallel those of probable and possible vascular dementia, with the important exception that instrumental activities of daily living should be normal or only mildly impaired.
- The concept of unstable vascular MCI was also introduced to account for individuals whose impairment may revert to normal during follow-up.

Unlike earlier classifications, a diagnosis of VCI does not require the presence of significant memory impairment as this is neither the most pronounced nor consistently observed cognitive deficit observed after stroke (Cumming, Marshall and Lazar 2013). Vascular cognitive impairment can impact the patient's mental ability, health and daily life, and is a major contributor to the burden caused by the long-term consequences of stroke due to intracerebral haemorrhage.

1.3. Quality of life vs health-related quality of life

There is a growing consensus that health related quality of life (HRQOL) is an important outcome measure as it reflects the impact of the disease from the perspective of the individual and can provide researchers with a more holistic picture of stroke recovery. However, there remains some question as to how this concept is best defined and measured (Christensen, Mayer and Ferran, 2009; Karimi and Brazier 2016).

The term quality of life (QOL) is thought to have derived from the WHO definition of health:

“a state of complete physical, mental and social well-being not merely the absence of disease” (World Health Organization 2014, p1)

Although many definitions for QOL exist, one point of agreement in the literature is that it is a multidimensional construct, comprising several domains. One of the most widely cited definitions for QOL comes from the World Health Organization Quality of Life Group. Quality of life is defined as an:

“individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment” (WHOQOL Group 1998, p1570).

This definition reflects the view that QOL refers to a subjective evaluation which is embedded in a cultural, social and environmental context. The individual's perception of quality is also key to quality of life assessment. Psychological processes, rather than circumstances alone, are central to an individual's experience of those aspects of life that contribute to its quality and to what extent.

While QOL is an all-inclusive concept incorporating all factors that are part of an individual's life, HRQOL includes only those factors that are part of an individual's health (Torrance 1987). Health-related quality of life refers to the specific impact of an illness, injury or medical treatment on an individual's QOL (Drotar 1998). The term HRQOL is not well defined in the literature and most definitions do not sufficiently differentiate the term from quality of life. However, although there is no single accepted definition of HRQOL, there is a substantial body of literature devoted to discussing and identifying important domains to be included within this construct. Spieth and Harris (1996) describe HRQOL as having four key domains: disease state and physical symptoms; functional status (the ability to perform a variety of age-appropriate daily activities); psychological functioning; and social functioning (the ability to maintain social relations). For this study, HRQOL will therefore be conceptualised as those areas of physical, psychological and social functioning that are likely to have been influenced by the experience of having a stroke due to haemorrhage.

1.4. Summary

This chapter has introduced the reader to the wider context of intracerebral haemorrhage, including its incidence, risk factors and diagnosis, and has set the scene for long-term management of this condition. An overview of the differences between mild cognitive impairment and dementia revealed that the concept of vascular cognitive impairment is the most appropriate term for any type of cognitive impairment (from mild cognitive impairment to dementia) that is associated with a vascular origin. This chapter then concluded with a brief discussion around the definitions for QOL and HRQOL, determining that health-related quality of life refers to the specific impact of an illness (such as intracerebral haemorrhage) on an individual's quality of life.

2. Intracerebral haemorrhage and cognitive decline: a review of the literature

While narrative reviews have highlighted the link between ICH and cognitive decline, there have been no literature reviews of cognitive impairment and dementia before and after ICH. I have addressed this gap by identifying and gathering all the available primary research on cognitive impairment and ICH in adults using thorough search methods. The quality of the identified research has been critically evaluated against methodological criteria and the results of studies have been systematically brought together in order to provide the best possible answer to the research questions.

2.1. Introduction

For any research to be justified, including literature reviews, the research questions must address what is important to patients (Pollock and Berge 2018). Cognitive impairment was recently identified as the first of the top ten research priorities relating to life after stroke by a priority setting project involving equal contributions from stroke survivors, carers, and health professionals (Pollock et al, 2012). Reliable data on long-term outcomes are needed to properly inform patients and their families, plan services for care following discharge from hospital and to help develop strategies to improve quality of life.

Stroke and dementia are closely related: they have similar risk factors, and each increases the risk of the other. In the systematic review by Pendlebury and Rothwell (2009) (previously discussed in Section 1.2.3), dementia appeared to be more frequent after ICH, but there were no studies of patients with ICH alone to identify either the specific predictors or the influence of the location of ICH, which is a crude indicator of the types of underlying small vessel disease.

Cognitive disorders are frequently seen after ICH yet until recently, very little was known about them as most studies had focused on ischaemic stroke survivors. Although three narrative reviews have highlighted the link between ICH and cognition, there have been no recent literature reviews of cognitive impairment and dementia before and after ICH (Murao, Rossi and Cordonnier 2013; Xiong et al, 2016; Planton et al, 2017a).

This literature review addresses the following research questions:

What is the incidence of pre-ICH cognitive impairment and dementia?

What is the prevalence of post-ICH cognitive impairment and dementia, in the short and long term?

What are the associated risk factors with pre- and post-ICH cognitive impairment and dementia?

2.2. Methods

2.2.1. Eligibility criteria

Peer reviewed studies were considered eligible for the present review if they met the criteria set out in Box 5.

Box 5: Eligibility criteria

Studies were considered eligible if they:

- (1) Assessed cognition in a cohort of patients with symptomatic intracerebral haemorrhage using a standardised measure or neuropsychological battery
OR
- (2) Tested cognition in a group of stroke patients, including some with intracerebral haemorrhage, and presented the results according to stroke subtypes
AND
- (3) Only included participants over 18 years
- (4) Were written in English
- (5) Had been published in a peer-reviewed journal

Studies were excluded if they:

- (6) Were a case report, dissertation/thesis or article with no primary data i.e. reviews, editorials, abstracts etc.

2.2.2. Search strategy

Studies were identified by searching the databases PubMed, CINAHL, Medline and PsychINFO on December 5th, 2017 with the search terms in Box 6. No constraint was placed on year of publication. To keep the literature review as up-to-date as possible, a second search was performed in November 2018 to look for any studies that had been published in the previous year.

Box 6: search terms

- 'cognition', 'cognitive', 'dementia' or 'neuropsychological' AND
- 'stroke', 'poststroke', 'prestroke', 'haemorrhag*' or 'hemorrhag*' NOT
- 'subarachnoid', 'ischemic' or 'ischaemic'.

After duplicates had been removed, all remaining articles were evaluated based on title and abstract. The remaining studies were then read in full and critically evaluated based on exclusion and inclusion criteria. The reference lists of selected studies and review articles were also examined to find relevant articles that might complement the database search.

2.2.3. Search results

The search strategy yielded 4252 articles. After 2747 duplicates had been removed, a further 1357 studies were excluded after screening the titles and abstracts. Once the remaining 148 had been read in full, 118 more articles were removed based on the eligibility criteria (the majority were removed as they did not present the results according to stroke subtypes). The screening of reference lists of included studies produced four additional articles, leaving a total of 34 articles for review. The second search, performed in November 2018, identified one more study for inclusion (Figure 2).

Ten studies measured the incidence of dementia or cognitive impairment before ICH (see Table 1), 15 provided data on the prevalence of dementia after ICH (see Table 2), and 13 on the prevalence of cognitive impairment after ICH (see Table 3). In addition, nine of the studies gave details regarding the predictive factors for cognitive decline (see Table 4).

2.2.4. Data synthesis and methodological quality assessment

Results of the included studies were analysed by making qualitative, descriptive summaries. Where possible, this literature review was reported in accordance with the PRISMA guidelines (Appendix 1).

The characteristics of the included articles are presented in Tables 1, 2 and 3. Data collection included study design, participant characteristics (including age, sex and number of participants), time since stroke, tools used to assess cognitive outcomes and results.

The methodological quality of all selected studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Appendix 2). It consists of 22 items, where each included item was scored one point. Although studies were not excluded based on the STROBE quality assessment, it was used to add to the critical analysis (Appendix 3).

Figure 2: Search and selection of eligible articles

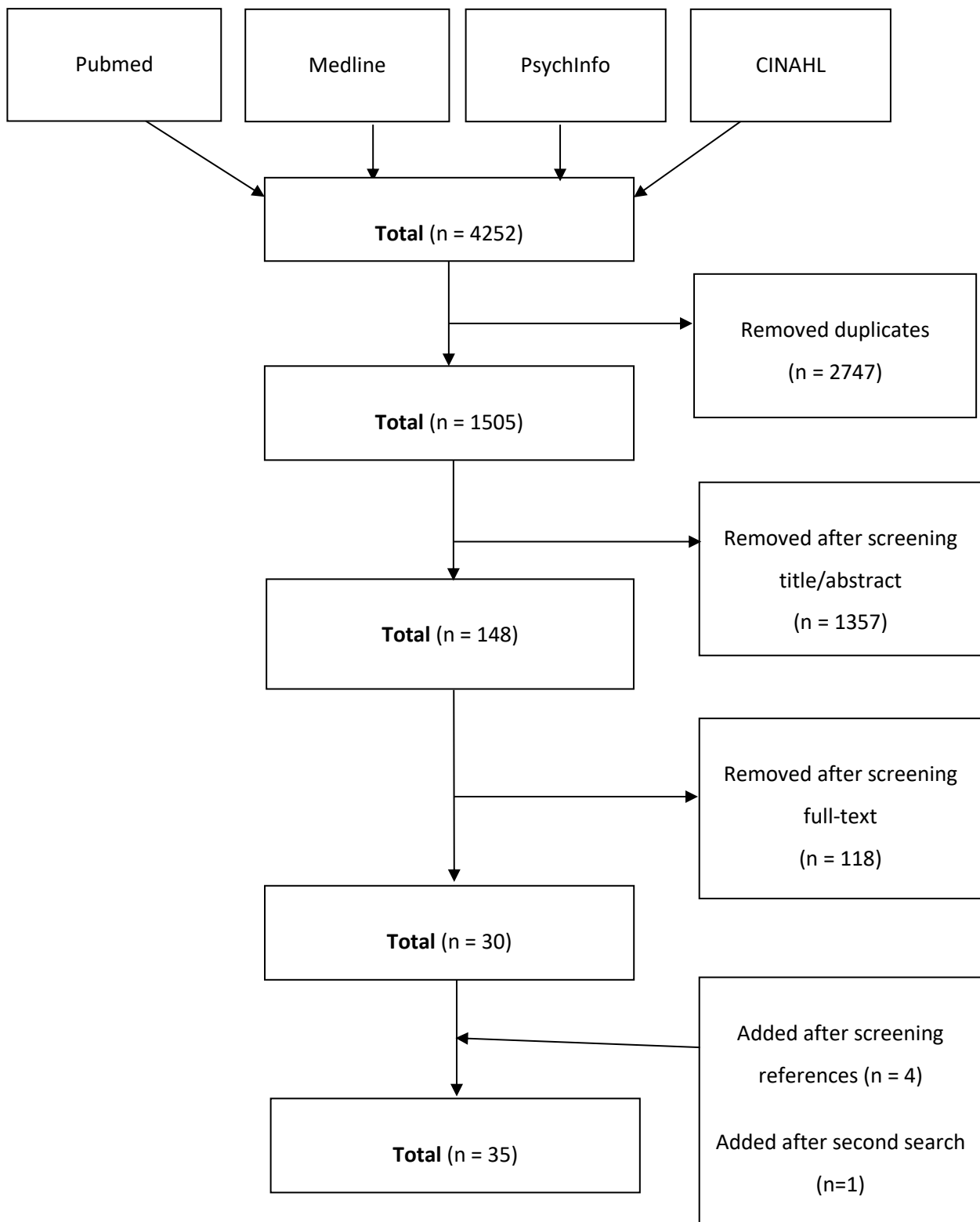


Table 1: Prevalence of dementia or cognitive impairment before ICH and characteristics of the studies including ICH patients

Author, country and year	Design, population and setting	Participants			Diagnosis of pre- existing dementia (method)	Prevalence of dementia before ICH	Prevalence of cognitive impairment before ICH	Prevalence of dementia before ischaemic stroke	STROBE score
		No. of stroke participants (ICH/IS)	Mean age (\pm SD)	Males					
Henon et al, 1997 France	Cross-sectional; IS and ICH; Hospital	25/177	75	48%	IQCODE	24%	N/A	15%	21
Barba et al, 2001 Spain	Cross-sectional; IS and ICH; Hospital	46/255	70.9 (\pm 13)	50%	IQCODE	13%	N/A	12%	20
Klimkowicz et al, 2002 Poland	Cross-sectional; IS and ICH; Hospital	32/218	65.1 (\pm 10.8)	43%	IQCODE	9%	N/A	12%	14
Smith et al, 2004 US	Longitudinal; ICH; Hospital	182	/	45-50%	IQCODE	N/A	23%	N/A	20

Author, country and year	Design, population and setting	Participants			Diagnosis of pre- existing dementia (method)	Prevalence of dementia before ICH	Prevalence of cognitive impairment before ICH	Prevalence of dementia before ischaemic stroke	STROBE score
		No. of stroke participants (ICH/IS)	Mean age (\pm SD)	Males					
Lefebvre et al, 2005 France	Cross-sectional; IS and ICH; Hospital	13/174	78.5	41%	IQCODE	23%	N/A	23%	22
Rost et al, 2008 US	Longitudinal; ICH; Hospital	629	/	54%	IQCODE	N/A	15%	N/A	21
Viswanathan et al, 2008 US	Longitudinal; ICH; Hospital	49	/	55%	IQCODE	N/A	20%	N/A	18
Cordonnier et al, 2010 France	Longitudinal; ICH; Hospital	417	72	52%	IQCODE	16%	14%	N/A	22
Laible et al, 2017 Germany	Cross-sectional; ICH; Hospital	89	70	58%	IQCODE	9%	18%	N/A	21

Author, country and year	Design, population and setting	Participants			Diagnosis of pre- existing dementia (method)	Prevalence of dementia before ICH	Prevalence of cognitive impairment before ICH	Prevalence of dementia before ischaemic stroke	STROBE score
		No. of stroke participants (ICH/IS)	Mean age (\pm SD)	Males					
Banerjee et al, 2018 UK	Cross-sectional; ICH; Hospital	166	69	63%	IQCODE	N/A	25%	N/A	22

IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly

Table 2: Prevalence of dementia after ICH and characteristics of the studies including ICH patients

Author, country and year	Design, population and setting	Participants			Duration after stroke (months)	Cognitive assessment	Diagnosis of dementia (criteria)	Exclusion of pre- existing dementia	Prevalence of dementia after ICH	Prevalence of dementia after IS	STROBE score
		No. of stroke participants (ICH/IS)	Mean age (\pm SD)	Males							
De Koning et al, 1998 Netherlands	Cross- sectional; IS and ICH; Hospital	35/203	69.2 (\pm 8.1)	60%	3-9	NPB	DSM-III	No	37%	19%	21
Barba et al, 2000 Spain	Cross- sectional; IS and ICH; Hospital	29/222	69 (\pm 13)	53%	3	NPB	DSM-IV	No	28%	30%	20
Madureira et al, 2001 Portugal	Cross- sectional; IS and ICH; Hospital	55/165	59 (\pm 12.7)	48%	3	NPB and MMSE	DSM- IV	Yes	5%	6%	20

Author, country and year	Design, population and setting	Participants			Duration after stroke (months)	Cognitive assessment	Diagnosis of dementia (criteria)	Exclusion of pre- existing dementia	Prevalence of dementia after ICH	Prevalence of dementia after IS	STROBE score
		No. of stroke participants (ICH/IS)	Mean age (\pm SD)	Males							
Henon et al, 2001 France	Longitudinal; IS and ICH; Hospital	19/150	/	53%	6-36	NPB	ICD-10	Yes	11%	23%	22
Tang et al, 2004 China	Cross- sectional; IS and ICH; Hospital	22/257	70.9 (\pm 9.6)	55%	3	MMSE	DSM- IV	No	18%	20%	20
Altieri et al, 2004 Italy	Longitudinal; IS and ICH; Hospital	4/170	71.3 (\pm 8.9)	69%	6-48	NPB	ICD-10	Yes	25%	22%	19
De Koning et al, 2005 Netherlands	Cross- sectional; IS and ICH; Hospital	19/77	70 (\pm 9)	62%	3-9	NPB and CAMCOG	DSM- IV	No	42%	35%	22

Author, country and year	Design, population and setting	Participants			Duration after stroke (months)	Cognitive assessment	Diagnosis of dementia (criteria)	Exclusion of pre- existing dementia	Prevalence of dementia after ICH	Prevalence of dementia after IS	STROBE score
		No. of stroke participants (ICH/IS)	Mean age (\pm SD)	Males							
Khedr, et al 2009 Egypt	Longitudinal; IS and ICH; Hospital	13/68	57.7 (\pm 5.2)	67%	3	MMSE CASI WMS-R	DSM-IV	Yes	24%	77%	20
Ihle-Hansen et al, 2011 Norway	Cross- sectional; IS and ICH; Hospital	16/159	72.0 (\pm 12.2)	51%	12	MMSE CDT TMT A and B 10-word test	ICD-10	Yes	44%	19%	18
Bejot et al, 2011 France	Cross- sectional; IS and ICH; Population	266/2847	72.9 (\pm 14.7)	47%	1	NPB	DSM- IV	No	11%	22%	22

Author, country and year	Design, population and setting	Participants			Duration after stroke (months)	Cognitive assessment	Diagnosis of dementia (criteria)	Exclusion of pre- existing dementia	Prevalence of dementia after ICH	Prevalence of dementia after IS	STROBE score
		No. of stroke participants (ICH/IS)	Mean age (\pm SD)	Males							
Garcia et al, 2013 France	Cross- sectional; ICH; Hospital	78	61.7 (\pm 14)	64	40	NPB and MMSE	DSM-IV	No	23%	N/A	21
Arauz et al, 2014 Mexico	Cross- sectional; IS and ICH; Hospital	14/93	56 (\pm 17.8)	62%	3	NPB	DSM-IV and NINDS- AIREN	Yes	14%	12%	21
Chaudhari et al, 2014 India	Longitudinal; IS and ICH; Hospital	12/90	59.4 (\pm 10.9)	74%	6	NPB and MMSE	NINDS- AIREN	Yes	33%	17%	19
Biffi et al, 2016 US	Longitudinal; ICH; Hospital	738 (6 months) 435 (longitudinal)	74.3 (\pm 12.1)	48%	3 and 6 months, and every 6 months	TICS	ICD-9	Yes	19% at 6 months (738)	N/A	22

Author, country and year	Design, population and setting	Participants			Duration after stroke (months)	Cognitive assessment	Diagnosis of dementia (criteria)	Exclusion of pre- existing dementia	Prevalence of dementia after ICH	Prevalence of dementia after IS	STROBE score
		No. of stroke participants (ICH/IS)	Mean age (\pm SD)	Males							
					for 4 years				32% at follow-up (435)		
Moulin et al, 2016 France	Longitudinal; ICH; Hospital	218	67.5	54%	6 and 12 months, and annually thereafter	MMSE and NPB	National Institute on Aging Alzheimer's Association criteria	Yes	14% at 12 months 28.3% at 4 years	N/A	22

CAMCOG- Cambridge Cognitive Examination; CASI: Cognitive Abilities Screening Instruments; CDT- Clock Drawing Test; DSM-III/IV: Diagnostic and Statistical Manual of Mental Disorders, Third and Fourth editions; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision; MMSE: Mini Mental State Examination; NINDS-AIREN: National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria for VaD; NPB: Neuropsychological test battery; TICS: Telephone Interview for Cognitive Status; TMT A and B- Trail Making Test A and B; WMS-R: Wechsler Memory Scale-Revised.

Table 3: Prevalence of cognitive impairment after ICH and characteristics of the studies including ICH patients

Author, country and year	Design, population and setting	Participants			Duration after stroke (months)	Diagnosis of CI (method)	Exclusion of pre-existing dementia?	Prevalence of cognitive impairment after ICH	Prevalence of cognitive impairment after IS	STROBE score
		No. of participant s (ICH/IS)	Mean age (\pm SD)	Males						
Patel et al, 2002 UK	Longitudinal; IS and ICH; Population	77/515	/	53%	3	MMSE	No	52%	38%	22
Tang et al, 2006 China	Cross- sectional: IS and ICH; Hospital	12/167	73 (\pm 7.5)	56%	3	MMSE	Yes	25%	22%	20
Nys et al, 2007 Netherlands	Cross- sectional; IS and ICH; Hospital	17/151	62.3 (\pm 16.8)	40%	1-2 weeks	NPB	Yes	~80% were impaired in at least 2 domains	~50% were impaired in at least 1 domain	22
Zhang et al 2012 China	Cross- sectional; IS	47/530	63.12 (\pm 9.8)	68%	3	MoCA Chinese- MMSE	Yes	40%	30%	22

Author, country and year	Design, population and setting	Participants			Duration after stroke (months)	Diagnosis of CI (method)	Exclusion of pre-existing dementia?	Prevalence of cognitive impairment after ICH	Prevalence of cognitive impairment after IS	STROBE score
		No. of participant s (ICH/IS)	Mean age (\pm SD)	Males						
	and ICH; Hospital					Battery of cognitive tests				
Douiri, Rudd and Wolfe, 2013 UK	Longitudinal; IS and ICH; Population	169/1309	/	53%	3	MMSE or Abbreviated Mental Test	No	40%	32%	21
Garcia et al, 2013 France	Cross- sectional; ICH; Hospital	48	60.8 (\pm 14.2)	65%	40	MMSE	Yes	77%	N/A	21
Arauz et al, 2014 Mexico	Cross- sectional; IS and ICH; Hospital	14/93	56 (\pm 17.8)	62%	3	NPB	Yes	71%	41%	21

Author, country and year	Design, population and setting	Participants			Duration after stroke (months)	Diagnosis of CI (method)	Exclusion of pre-existing dementia?	Prevalence of cognitive impairment after ICH	Prevalence of cognitive impairment after IS	STROBE score
		No. of participant s (ICH/IS)	Mean age (\pm SD)	Males						
Chaudhari et al, 2014 India	Longitudinal; IS and ICH; Hospital	12/90	59.4 (\pm 10.9)	74%	6	NPB and MMSE	Yes	50%	44%	19
Tveiten et al, 2014 Norway	Cross- sectional; ICH; Hospital	44	70.8 (\pm 12.8)	43%	46	MoCA <24 MoCA <26	No	61% 71%	N/A	22
Jacquín et al, 2014 France	Cross- sectional; IS and ICH; Hospital	16/204	66.1 (\pm 16.6)	56%	3	MMSE MoCA	Yes	31%	49%	20
Qu et al, 2015 China	Cross- sectional; IS and ICH; Community	62/518	67.91 (\pm 16.6)	46%	54	MocA MMSE	Yes	87%	80%	20

Author, country and year	Design, population and setting	Participants			Duration after stroke (months)	Diagnosis of CI (method)	Exclusion of pre-existing dementia?	Prevalence of cognitive impairment after ICH	Prevalence of cognitive impairment after IS	STROBE score
		No. of participant s (ICH/IS)	Mean age (\pm SD)	Males						
Benedictus et al, 2015 France	Longitudinal; ICH; Hospital	167	64	59%	48	MMSE	Yes	37%	N/A	22
Planton et al, 2017b France	Cross- sectional; ICH; Hospital	40	65.8- 70.7	50%	4	MMSE and NPB	Yes	87.5%	N/A	22

MoCA: Montreal Cognitive Assessment; MMSE: Mini Mental State Examination; NPB: Neuropsychological test battery

Table 4: Risk factors for vascular cognitive disorders before and after ICH

Author, year	Is cognitive decline assessed pre- or post-ICH?	Risk factors
Viswanathan et al, 2008	Pre-ICH	Chronic tissue disruption (Odds ratio (OR) per 1×10^{-4} mm ² /s increase=2.45, 95% CI 1.11 to 5.40; $p=0.04$)
Cordonnier et al, 2010	Pre-ICH	<u>In lobar intracerebral haemorrhage:</u> Increasing age (OR 1.09 per year; 95% CI 1.02-1.15) Less than 8 years of education (OR 8.37; 95% CI 1.91-36.65) Cortical atrophy (OR 3.34 per step; 95% CI 1.40-7.96) <u>In deep intracerebral haemorrhage:</u> Old territorial vascular lesions (OR 4.52; 95% CI 1.18-17.42) Leucoaraiosis (OR 4.11 per step; 95% CI 1.73-9.75)
Liable et al, 2017	Pre-ICH	Previous stroke or TIA (OR 18.29; 95%-CI 1.945–172.033, $p=.011$) Hematoma volume (OR 0.90 per ml; 95%-CI 0.812–0.991, $p=.033$)
Banjeree et al, 2018	Pre-ICH	Meets modified Boston criteria for probable CAA (OR 4.01; 95% CI 1.53-10.51) Increasing CAA score (OR 1.42 per point increase; 95% CI 1.03-1.97) Cortical superficial siderosis (OR 4.08; 95% CI 1.28-13.05)
Garcia et al, 2013	Post-ICH	Higher levels of disability at discharge (OR 3.5; 95% CI 1.7-6.9, $p<.001$) Haemorrhage volume ($p =.07$).

Author, year	Is cognitive decline assessed pre- or post-ICH?	Risk factors
Tveiten et al, 2014	Post-ICH	Age (OR 2.4 per 10 years; $p=0.010$) Lobar ICH location (OR 14.1; $p=0.016$)
Benedictus et al, 2015	Post-ICH	Previous stroke or transient ischemic attack (β [SE], -0.55 [0.23]; $p<0.05$) Pre-existing cognitive impairment (β [SE], -0.56 [0.25]; $p<0.01$) Severity of cortical atrophy (β [SE], -0.50 [0.19]; $p<0.01$) <u>In patients without pre-existing cognitive impairment:</u> Severity of cortical atrophy (β [SE], -0.38 [0.17]; $p<0.05$)
Biffi et al, 2016	Post-ICH	<u>Early onset dementia:</u> Larger hematoma size (hazard ratio [HR], 1.47 per 10-mL increase; 95% CI, 1.09-1.97; $p<.001$ for heterogeneity) Lobar ICH location (HR, 2.04; 95% CI, 1.06-3.91; $p=.02$ for heterogeneity) <u>Delayed onset dementia:</u> Educational level (HR, 0.60; 95% CI, 0.40-0.89; $p<.001$ for heterogeneity) Mood symptoms (HR, 1.29; 95% CI, 1.02-1.63; $p=.01$ for heterogeneity) White matter disease (HR, 1.70; 95% CI, 1.07-2.71; $p=.04$ for heterogeneity)
Moulin et al, 2016	Post-ICH	<u>Whole cohort (lobar and deep):</u> Lobar ICH location (subhazard ratio (SHR): 2.22, 95% CI: 1.30–3.79)

Author, year	Is cognitive decline assessed pre- or post-ICH?	Risk factors
		<p>Severe leukoaraiosis (SHR for score 3: 2.88, 95% CI: 1.63–5.07)</p> <p>History of previous stroke or TIA (SHR: 2.57, 95% CI: 1.43–4.62) older age (SHR per 10- year increase: 1.84, 95% CI: 1.43–2.38)</p> <p>More severe stroke (as recorded by NIHSS) (SHR per 5- point increase: 1.20, 95% CI: 1.05–1.36)</p> <p>New stroke or TIA during follow-up (SHR: 3.22, 95% CI: 1.27–8.15)</p> <p><u>In subgroup of patients with lobar ICH:</u></p> <p>Severe leukoaraiosis (SHR for score ≥ 3: 2.70, 95% CI: 1.35–5.38)</p> <p>Older age (SHR per 10-year increase: 1.75, 95% CI: 1.01–1.11)</p> <p>NIHSS score (SHR 1 per 5-point increase: 1.42, 95% CI: 1.16–1.74)</p> <p>Increased cortical atrophy score (SHR per 1-point increase: 2.33, 95% CI: 1.25–4.35)</p> <p>Pre-existing cognitive impairment (SHR: 3.84, 95% CI: 1.79–8.20)</p> <p><u>In patients with brain MRI (lobar and deep):</u></p> <p>Disseminated superficial siderosis (SHR: 7.45, 95% CI: 4.27–12.99)</p> <p>Increasing cortical atrophy score (SHR per 1-point increase: 2.61, 95% CI: 1.70– 4.01)</p> <p>Higher number of cerebral microbleeds (five or more) (SHR for > 5: 2.33, 95% CI: 1.38–3.94)</p>

Author, year	Is cognitive decline assessed pre- or post-ICH?	Risk factors
		<p><u>In patients with brain MRI (lobar only):</u></p> <p>Disseminated superficial siderosis (SHR: 7.25, 95% CI: 3.76–13.97)</p> <p>Cortical atrophy (SHR per 1-point increase: 6.68, 95% CI: 2.29–19.50)</p> <p>Old macro-haemorrhages (SHR: 3.6, 95% CI: 1.74–7.44)</p>

2.3. Findings

2.3.1. Cognitive decline before ICH

Until recent years, most of our knowledge on cognitive decline prior to stroke relied on cohorts which only or predominantly included ischaemic strokes (Pendlebury and Rothwell 2009). Ten studies were found that reported data on pre-existing cognitive decline in patients with ICH. Six included intracerebral haemorrhage patients only, while the remaining 4 included both ischaemic and haemorrhagic stroke sub-types. Pre-existing cognitive decline is usually estimated with the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) (Jorm 1994). This questionnaire is rated by a relative who is asked to compare the participant's ability to perform a list of daily cognitive tasks involving memory, praxis, calculation, or reasoning with his or her baseline 10 years prior to the index event. Of the ten studies that assessed the frequency of pre-existing cognitive decline in patients with ICH, all used the IQCODE.

In the four studies that reported data on a sub-set of patients with ICH, 940 participants were included (116 with ICH and 824 with ischaemic stroke), where the number of participants with ICH ranged from 13-46. The small numbers of ICH survivors may be somewhat explained by the low frequency (10-15% of all strokes) and high mortality rate (approximately 40% in the first month) of ICH. Prevalence of dementia prior to stroke was 9-24% before intracerebral haemorrhage, and 12-23% before an ischaemic stroke (Henon et al, 1997; Barba et al, 2001; Klimkiewicz et al, 2002; Lefebvre et al, 2005).

To date, six studies have examined the frequency of pre-existing cognitive decline in cohorts purely comprised of intracerebral haemorrhage participants. Four assessed pre-existing cognitive impairment (Smith et al, 2004; Rost et al, 2008; Viswanathan et al, 2008; Banjeree et al, 2018), and two gave figures for both pre-existing cognitive impairment and dementia (Cordonnier et al, 2010; Laible et al, 2017).

In a recent prospective study which focused on pre-existing cognitive impairment and dementia in a consecutive cohort of patients with ICH, cognitive status was assessed within 48 hours of stroke onset using the short version of the IQCODE (Cordonnier et al, 2010). Patients who scored between 53 and 63 were classified as having cognitive impairment without dementia, and patients who scored over 63 were thought to have pre-existing

dementia. Of 417 consecutive patients, 14% (58 patients) were considered to have cognitive impairment before ICH and 16% (65 patients) had pre-existing dementia. Among patients with lobar ICH, the prevalence of pre-existing dementia was 23%, compared to 12% in patients who had deep haemorrhages, and 9% in the fossa ICH group. In a similar study, Laible et al (2017) recruited a cohort of 89 ICH patients in the acute phase of stroke. IQCODE indicated cognitive impairment in 16 (18%) patients prior to their ICH, of which 8 (9%) were found to have pre-existing dementia.

Three other studies describing levels of cognitive impairment before ICH have found a prevalence of 15% in a cohort of 629 patients (Rost et al, 2008); 20% in a cohort of 49 ICH patients meeting the Boston criteria¹ for probable or possible CAA (Viswanathan et al, 2008); and 23% in a cohort of 182 lobar ICH patients aged 55 years and above (Smith et al, 2004). While Smith et al (2004) found more severe white matter disease as seen on CT to be independently associated with cognitive impairment before ICH, in the study by Viswanathan et al (2008), chronic tissue disruption (as measured by mean apparent diffusion coefficient (ADC) on MRI) was the only variable strongly associated with pre-existing cognitive decline. Although Viswanathan et al (2008) were unable to find a correlation between MRI markers of CAA and pre-existing decline other than mean ADC, this may reflect the small sample size. A recent study from Banjee et al (2018) aimed to investigate the association between cognitive impairment before ICH and MRI markers of cerebral amyloid angiopathy. A total of 166 patients with neuro-imaging confirmed ICH were included in the study. In analysis adjusted for clinical and demographic variables, cognitive impairment before ICH was statistically significantly associated with meeting the modified Boston criteria for probable CAA at presentation, a higher composite CAA score and cortical superficial siderosis.

Conclusion: In the studies that reported data on a sub-set of patients with ICH, prevalence of dementia prior to stroke was similar in both ICH and ischaemic stroke subgroups, with up to one in four patients suffering from pre-existing dementia. Studies examining the frequency

¹A system that uses clinical, imaging and pathological information to categorise the probability of cerebral amyloid angiopathy into 'definite', 'probable' and 'possible' (Knudsen et al, 2001)

of pre-existing cognitive decline in cohorts purely comprised of intracerebral haemorrhage participants found the prevalence of pre-existing cognitive decline to be 14-25%, and pre-existing dementia 9-16%. Risk factors for cognitive decline prior to ICH included neuroimaging markers for CAA.

2.3.2. Dementia after ICH

Fifteen studies have reported data on dementia after ICH. Three included intracerebral haemorrhage patients only, while the remaining 12 included both ischaemic and haemorrhagic stroke sub-types.

Within the twelve studies that reported data on dementia after stroke in a small subgroup of patients with ICH, 5,005 participants were included (504 with ICH and 4,501 with ischaemic stroke), where the number of participants with ICH ranged from 4-266 (de Koning et al, 1998; Barba et al, 2000; Madureira, Guerreiro and Ferro 2001; Henon et al, 2001; Tang et al, 2004; Altieri et al, 2004; de Koning et al, 2005; Khedr et al, 2009; Ihle-Hansen et al, 2011; Bejot et al, 2011; Arauz et al, 2014; Chaudhari et al, 2014).

Within these studies, the incidence of dementia after stroke was 5-44% for ICH patients, and 6-77% for ischaemic stroke patients. However, five studies did not exclude pre-existing cognitive decline, allowing for a possible overestimation in the prevalence of new-onset dementia. In addition, the timing and methods for cognitive assessments varied. One study assessed cognition in the first month after stroke; nine between 3 months and 1 year; and two between 1 and 4 years. With regards to the methods of assessment: 9 studies performed detailed cognitive testing using a comprehensive neuropsychological test battery and the remaining three studies used a variety of brief cognitive assessments.

To date, only three studies dedicated to patients with ICH have reported data on dementia prevalence (Garcia et al, 2013; Moulin et al, 2016; Biffi et al 2016). In a single centre retrospective study, among the 78 ICH survivors who were recruited, 48 underwent a comprehensive neuropsychological assessment (Garcia et al, 2013). At a mean follow-up time of 41 months, dementia was observed in roughly one in four patients according to the DSM-IV (23%). In bivariate analysis, possible risk factors for dementia were haemorrhage volume, residency in a nursing home and higher levels of disability (Rankin score of more

than 1). Cognitive impairment without dementia was seen in 37 patients (77%) and was diagnosed when patients showed a significant impairment in one cognitive domain without significant impairment to activities of daily living. Although this study is of value, only one patient was identified as having pre-existing dementia. It is likely that this number was underestimated due to the use of a retrospective, cross-sectional design.

A recent prospective observational study with a median follow-up of 6 years recruited a cohort of 218 ICH survivors without pre-existing dementia (Moulin et al, 2016). The incidence of new-onset dementia was 14% within the first year, 20% at 2 years, 24.5% at three years, and 28% at 4 years. Interestingly, the incidence of new-onset dementia was more than two times higher in patients with lobar (23.4%) versus non-lobar (9.2%) intracerebral haemorrhage. This difference emerged when patients were first assessed at 6 months after stroke onset, suggesting that the initial stroke may have been the main contributor to dementia soon after onset. For patients who developed dementia later during follow-up, dementia incidence rates were similar between lobar and non-lobar ICH. This is likely to be attributable to the underlying small vessel diseases (Al-Shahi Salman et al, 2016).

In addition to lobar location of the ICH, multivariable analysis in the whole cohort identified severe leukoariosis, history of previous stroke or TIA, older age, more severe stroke (as recorded by NIHSS) and the occurrence of any new stroke or TIA during follow-up as independent risk factors for new-onset dementia.

Moulin et al (2016) also investigated radiographical biomarkers in patients with available brain MRI data (188 patients) and found that disseminated superficial siderosis, increasing cortical atrophy score and a higher number of cerebral microbleeds (five or more), were independently associated with dementia. When this analysis was repeated in the subgroup of patients with lobar ICH, the results revealed that disseminated superficial siderosis, cortical atrophy and old macro-haemorrhages were risk factors for new-onset dementia. Although the results were fairly consistent between the whole cohort of patients with MRI and those with lobar ICH, we were not told whether small vessel disease biomarkers on brain MRI differed between lobar and non-lobar intracerebral haemorrhage (Al-Shahi Salman et al, 2016).

Most recently, Biffi et al (2016) recruited 738 participants without pre-existing dementia to a longitudinal study comparing risk factors for early and delayed dementia after ICH.

Cognitive performance was measured using the modified Telephone Interview for Cognitive Status (TICS- a brief test of cognitive function that can be performed over a telephone interview) test at 3 and 6 months after ICH, and then every 6 months thereafter in a subset of patients for whom long-term follow-up data were available (mean follow-up duration of 47 months). In this study, dementia was characterised by a low TICS score or an ICD-9 code (a system used by physicians to classify and code diagnoses and symptoms) consistent with dementia. Early dementia was defined as an onset within the first 6 months after ICH, with delayed dementia being an onset beyond that time. Among the 738 patients, 140 (19%) developed dementia within the first 6 months. Patients without dementia at 6 months (435 patients) were then followed up longitudinally with an estimated yearly incidence of dementia of 5.8%. Two hundred and seventy-nine of the 738 (37.8%) participants developed dementia at some point during follow-up. Most notable however were the differing risk factors for early vs late dementia. Large haematoma size and lobar location of ICH were identified as risk factors for early (but not delayed) incident dementia, reflecting the findings of Moulin et al (2016) which suggested that the initial stroke may have been the main contributor to early onset dementia. Level of education, white matter disease (as seen on CT) and history of a mood disorder, were important in predicting delayed dementia. Although the definition of dementia may have resulted in an overestimation of its incidence, these findings emphasise that dementia, or at the very least cognitive decline, is a common complication after ICH. Risk of delayed onset dementia had little to no association with the acute bleeding event. The delayed onset in a large percentage of individuals suggest that ICH may be a marker of an underlying process as opposed to an event that precipitates worsened decline.

Conclusion: Within the twelve studies that reported data on dementia after stroke in a small subgroup of patients with ICH, the incidence of dementia after stroke was higher in the ischaemic stroke subgroup. In the three studies dedicated to patients with ICH, dementia was observed in 23-38% of patients (mean follow-up time of 4 years). In one of the studies, the incidence of new-onset dementia was more than two times higher in patients with lobar versus non-lobar intracerebral haemorrhage. Risk factors for dementia after ICH suggest that that the initial stroke may have been the main contributor to early onset dementia while late-onset dementia (after 6 months) is likely to be attributable to the underlying small vessel diseases.

2.3.3. Cognitive impairment after ICH

Ten additional papers were identified that investigated the prevalence and risk factors for cognitive impairment after stroke in ICH patients (Patel et al, 2002; Tang et al, 2006; Nys et al, 2007; Zhang et al, 2012; Douiri, Rudd and Wolfe, 2013; Tveiten et al, 2014; Jacquin et al, 2014; Qu et al, 2015; Benedictus et al, 2015; Planton et al, 2017b). Seven of these studies included both ischaemic and haemorrhagic stroke sub-types, while the remaining three only recruited participants with ICH.

From the seven studies investigating the prevalence of cognitive impairment after an ischaemic or haemorrhagic stroke, a total of 3,794 participants were recruited (400 with ICH and 3,394 with ischaemic strokes). Prevalence of cognitive impairment ranged from 25-87% after ICH, and 22-80% after ischaemic stroke. Once again, timing and methods of assessment varied between studies. One study assessed cognition at 1-2 weeks; five assessed participants at 3 months; and one at 4.5 years after the index event. While two studies relied solely on brief cognitive assessments for their diagnosis of cognitive impairment, one study made use of a full neuropsychological test battery and four studies used a combination of brief assessments. Two studies did not exclude pre-existing dementia prior to assessment.

In addition to the study by Garcia et al (2013) (described above), only three further studies could be found that investigated the frequencies and patterns of cognitive impairment after stroke in a dedicated ICH cohort (Tveiten et al, 2014; Benedictus et al, 2014; Planton et al, 2017b). In a Norwegian study which aimed to assess long-term functional outcome after ICH, among the 44 patients with ICH that could be assessed with the Montreal Cognitive Assessment (MoCA), 61% reported cognitive impairment during follow-up (median follow-up time 3.8 years) (Tveiten et al, 2014). Factors independently associated with cognitive impairment were age and lobar ICH location. However, data on cognition before the ICH were not available.

A prospective study was recently conducted to determine prognostic factors for cognitive decline in ICH patients (Benedictus et al, 2015). At 6 months after stroke onset, 167 patients without pre-existing dementia were followed up for a median time of 4 years. Thirty-seven percent of patients exhibited cognitive decline during follow-up, where the annual change in Mini Mental State Examination (MMSE) scores was used as a marker of cognitive loss. Multivariate analysis showed that previous stroke or TIA, pre-existing cognitive impairment

and severity of cortical atrophy were all independent prognostic factors for cognitive decline. In patients without pre-existing cognitive impairment (139 patients), cerebral cortical atrophy was the only prognostic factor for cognitive decline after ICH. Interestingly, ICH characteristics (i.e. volume, location, multiple ICHs) were not associated with cognitive decline. Instead, the authors demonstrated that the risk of cognitive decline after ICH was associated with factors already present before the ICH occurred. One of the limitations of this study was the use of the MMSE as an outcome measure. Although the MMSE is a widely accepted test for the evaluation of cognition in the elderly, it may lack the sensitivity to assess for vascular cognitive impairment.

Finally, a recent study by Planton et al (2017b) aimed to investigate the frequency and patterns of vascular cognitive disorders in patients with CAA related and deep ICH. They recruited 20 lobar ICH patients with possible or probable CAA (according to the modified Boston criteria), and 20 deep ICH patients. Mild (decline in one or more cognitive domains, with test performance between 1 and 2 standard deviations below the norm) and major (decline in one or more cognitive domains, with test performance 2 or more standard deviations below the norm) vascular cognitive disorders were observed respectively in 87.5% and 2.5% of all ICH patients. Every patient in the CAA group had mild vascular cognitive disorders. However, no significant difference was observed in cognitive functioning between the two ICH groups.

Conclusion: From the seven studies investigating the prevalence of cognitive impairment after an ischaemic or haemorrhagic stroke, prevalence of cognitive impairment was similar in both ICH and ischaemic stroke subgroups, where up to four-fifths of patients had cognitive impairment after their stroke. Of the four studies that could be found that investigated cognitive impairment after stroke in a dedicated ICH cohort, the frequency of cognitive impairment ranged from 37-88%. An assessment of risk factors among this group indicated that the risk of cognitive decline after ICH was associated with factors already present before the ICH occurred.

2.4. Discussion

From the available literature on cognitive decline before ICH, data suggest that pre-existing cognitive impairment and dementia are not uncommon. The finding that the prevalence of pre-existing dementia was seen more frequently in patients with lobar ICH is an interesting one. In the study by Cordonnier et al (2010), available post-mortem data from 4 patients with pre-existing dementia and lobar haemorrhages confirmed definite CAA associated with Alzheimer's Disease pathology. In the one autopsied patient with pre-existing dementia and deep ICH, severe small vessel disease was found without Alzheimer's Disease or CAA, enabling a diagnosis of pure vascular dementia. Although only 5 patients with pre-existing dementia were autopsied, these findings support the notion that pre-existing dementia may be the consequence of the different underlying pathologies; a vascular process in non-lobar ICH and Alzheimer's Disease pathology with CAA in lobar ICH. These findings are echoed in the study from Banjee et al (2018) who found that MRI neuroimaging markers of CAA were associated with pre-ICH cognitive impairment. This would appear to provide evidence that the small vessel disruption caused by CAA makes an important contribution to pre-existing cognitive impairment.

From the studies assessing risk factors for cognitive impairment and dementia after ICH, most factors were already present when the ICH occurred. Although there may be a haematoma volume effect on cognition in the acute stage, in the long-term it seems to be a process of ongoing cognitive impairment. The underlying small vessel disease that caused the bleeding, rather than the bleed itself, may therefore be responsible for future development of cognitive decline.

This literature review benefited from thorough ascertainment of a large number of relevant studies, using multiple electronic databases, in an attempt to be comprehensive and avoid reporting bias. Studies underwent a comprehensive critical appraisal and judgement relating to whether there were any potential risks of bias within the study. The average methodological quality score was 20, with most studies attaining a methodological score of between 20 and 22, suggesting that the quality and reporting of included studies was at a high standard.

In the most recent narrative review from Planton et al (2017a), the authors concluded that future ICH outcome research should include longitudinal and extensive cognitive

examinations, which separate the acute bleeding events from any potential underlying disease process. The researchers also emphasised the need for future studies to investigate behavioural, mood and quality of life data in ICH, as these are currently lacking.

In addition to the above, there have been no qualitative studies designed specifically to examine cognitive decline after ICH. Performance on cognitive assessments is not likely to capture the full experience of cognitive impairment. Qualitative interviews with ICH survivors and their carers could help provide much needed insight into the lived experience of cognitive decline, and the impact that it has on daily life and relationships.

3. The influence of cognitive impairment on health-related quality of life after stroke: a review of the literature

Although many studies have sought to investigate the potential impact that cognitive impairment can have on health-related quality of life after stroke, an overview of this literature is still lacking. I have addressed this gap by identifying and gathering all the available primary research investigating the relationship between cognitive impairment and HRQOL after stroke using thorough search methods. The quality of the identified research has been critically evaluated against methodological criteria and the results of studies have been systematically brought together in order to provide the best possible answer to the research question.

3.1. Introduction

Traditionally, studies researching the long-term consequences of stroke have focused their attention on clinical outcomes such as recurrent stroke and survival. Although this is of great importance to physicians and other healthcare professionals, in recent years, researchers have begun to select outcomes that matter most to patients and their families (Pollock et al, 2012; Carod-Artal et al, 2000; Rincon 2013). Health-related quality of life refers to those aspects of quality of life affected by disease. HRQOL can be drastically reduced after stroke given its sudden nature and the inability of patients and their families to adjust and cope with the long-term complications. There is a growing consensus that HRQOL is an important outcome as it reflects the impact of the disease from the perspective of the individual and can provide researchers with a more holistic picture of stroke recovery (Christensen, Mayer and Ferran 2009).

Many factors are thought to influence quality of life after stroke. Studies assessing HRQOL in stroke patients have identified: depression, fatigue, social support, functional status, motor impairment, anxiety, disability, dementia, neglect, stroke severity, age, incontinence, female sex, social participation, reduced activities of daily living, side of lesion, number of co-morbidities and cognitive impairment as determinants of poor quality of life (King, 1996; Carod-Artal et al, 2000; Sturm et al, 2004; Haacke et al, 2006; Patel et al, 2007; Franceschini et al, 2010; Hilari et al, 2010; Howitt et al, 2011; Meyer et al, 2010; Kreiter et al, 2013; Tjahjadi

et al, 2013; Dhamoon et al, 2014; Chen-Min et al, 2015). Although many studies have sought to investigate the impact of cognitive impairment on HRQOL after stroke, an overview of this literature is still lacking. The only available review describing the influence of cognitive impairment on HRQOL in this cohort did not focus on stroke, but rather neurological disease in general, and consequently missed some of the relevant studies (Mitchell et al, 2010). Although the focus of this thesis is intracerebral haemorrhage, due to the lack of available literature (no studies could be found assessing the relationship between cognitive impairment and HRQOL with a dedicated intracerebral haemorrhage cohort), this review has included all stroke sub-types. This literature review therefore addresses the following research question:

What is the relationship between cognitive impairment and HRQOL after stroke?

3.2. Methods

3.2.1. Eligibility criteria

Peer reviewed studies were considered eligible for the present review if they met the criteria set out in Box 7.

Box 7: Eligibility criteria

Studies were considered eligible if:

- (1) More than 50% of the study population had a stroke
- (2) All participants were over 18 years
- (3) One of the outcomes was HRQOL, assessed using a standardised measure
- (4) One of the determinants studied had to give an indication of cognitive impairment, assessed with a standardised measure or neuropsychological battery
- (5) The article was written in English
- (6) They were published in a peer-reviewed journal

Studies were excluded if they:

- (7) Were a case report, dissertation/thesis or article with no primary data i.e. reviews, editorials, abstracts etc

3.2.2. Search strategy

Studies were identified by searching the databases PubMed, Embase, CINAHL and PsychINFO on September 11, 2017. No constraint was placed on year of publication. The search combined a 'stroke' domain with a 'HRQOL' outcome and 'cognitive impairment' determinant (see Box 8).

Box 8: Search terms

- cognitive impairment OR memory OR dementia OR cognit* OR MMSE OR mini-mental state examination (Abstract) **AND**
- stroke OR strokes OR CVA OR CVAs OR vascular accident OR vascular accidents OR cerebrovascular OR brain infarction OR brain infarctions OR cerebral infarction OR cerebral infarctions OR ischemic OR ischaemic OR haemorrhage OR hemorrhage OR poststroke OR poststroke (Title) **AND**
- quality of life OR QOL OR life quality OR life qualities OR health-related quality of life OR HRQOL OR perceived health OR health status OR wellbeing OR well-being (Abstract)

After duplicates had been removed, all remaining articles were evaluated based on title and abstract. The remaining studies were then read in full and critically evaluated based on exclusion and inclusion criteria. The reference lists of selected studies were also examined to find relevant articles that might complement the database search.

3.2.3. Search results

The search strategy yielded 2402 articles. After 1202 duplicates had been removed, a further 1089 studies were excluded after screening the titles and abstracts. Once the remaining 111 had been read in full, 63 more articles were removed based on the eligibility criteria. The screening of reference lists of included studies produced six additional articles, leaving a total of 54 articles for review (Figure 3). 32 studies measured global cognitive functioning against overall HRQOL score (see Table 5), while the remaining 22 studies assessed cognitive and/or HRQOL domains (see Table 6).

3.2.4. Data synthesis and methodological quality assessment

Results of the included studies were analysed by making qualitative, descriptive summaries. Where possible, this review has been reported in accordance with the PRISMA guidelines (Appendix 1).

The characteristics of the included articles are presented in Tables 5 and 6. Data collection included study design, participant characteristics (including age, sex and number of participants), time since stroke onset (follow-up), outcome measures and results.

The methodological quality of all selected studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Appendix 2). Each item was scored one point, with the maximum possible score being 22. Although studies were not excluded based on the STROBE quality assessment, it was used to add to the critical analysis (Appendix 4).

Figure 3: Search and selection of eligible articles

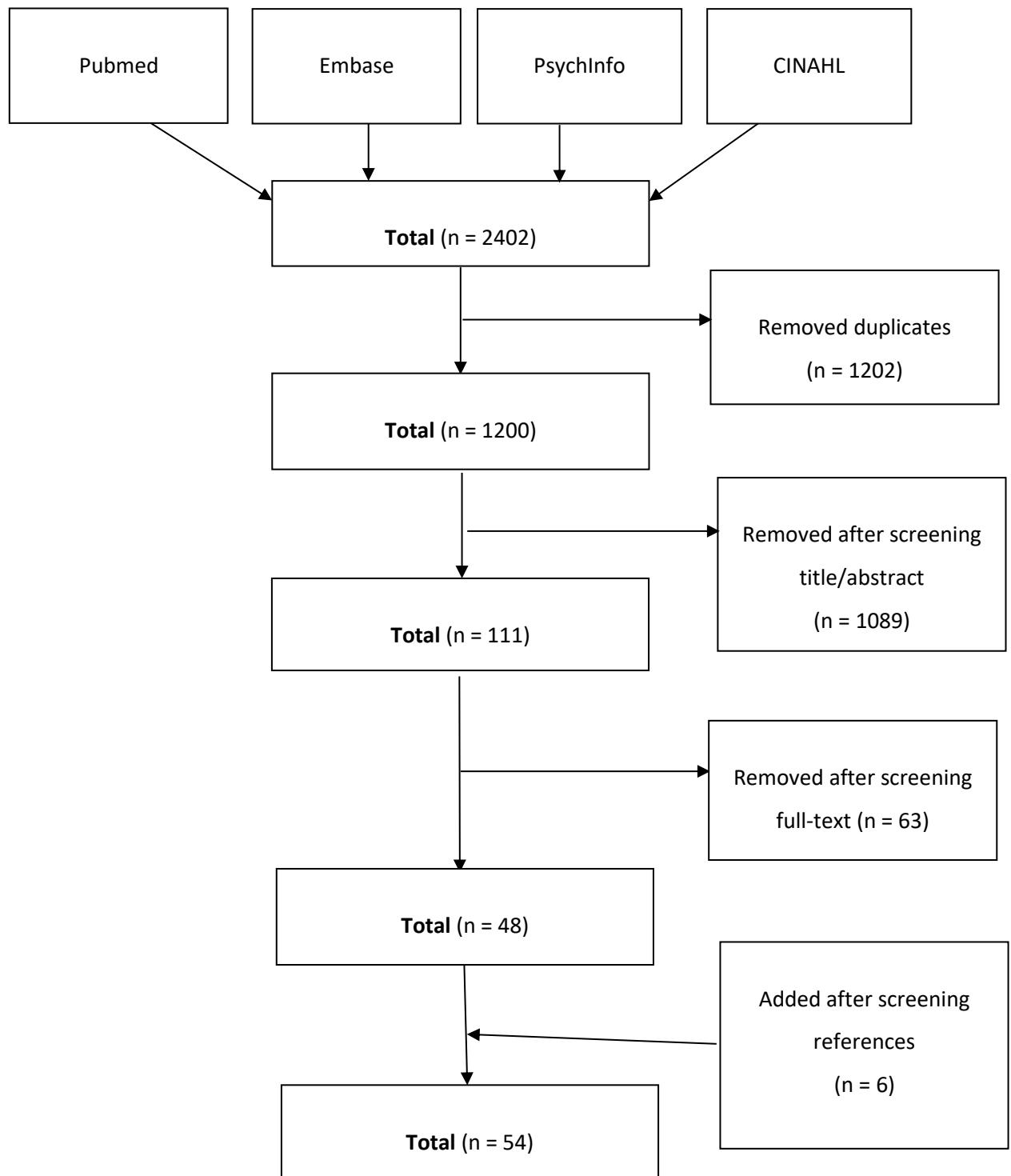


Table 5: Characteristics of studies measuring global cognition and overall HRQOL

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Adamit, T Israel 2015	Longitudinal; Mild ischaemic stroke; Home assessment	249	68.6 (\pm 9.9)	57%	3 months	SIS v2.0	MoCA	$r = 0.421$ $p < 0.001$	22
Alvarez- Sabin, J Spain 2016	Randomised, controlled trial; Ischaemic stroke; Outpatient	163	67.5 (\pm 10.7)	49%	2 years	EQ-5D	NPB	NR	16
Ankolekar, S UK 2014	Randomised, controlled trial; Ischaemic and haemorrhagic; Telephone interview	1572	69 (\pm 12)	60%	90 days	EQ-5D	MMSE TICS	$r = 0.507$ (MMSE) $r = 0.519$ (TICS) $p < 0.001$	21

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Canuto, O Brazil, 2016	Cross-sectional; Ischaemic and haemorrhagic; Outpatient	77	57.3 (\pm 17.2)	52%	NR	SS-QOL	MMSE	$r = 0.4$ $p = 0.0$	20
Chen-Min, C Taiwan 2015	Cross-sectional; Ischaemic and haemorrhagic; Rehabilitation centre	119	54.89 (\pm 10.5)	74%	6 months	SIS v3.0	MMSE	$\beta = 1.310$ $p < 0.001$	20
Chou, C Taiwan 2015	Cross-sectional; Ischaemic and haemorrhagic; Rehabilitation centre	134	59.02 (\pm 11)	71%	nr	SS-QOL-12 SS-QOL-8	MMSE	NS	15

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Cumming, T.B Australia 2014	Longitudinal; Ischaemic and haemorrhagic; Home assessment	56	72.1 (\pm 13.9)	73%	3 and 12 months	AQOL	NPB	β = -0.103 p = 0.021	21
Dhamoon, M.S US 2010	Longitudinal; Ischaemic stroke; Outpatient	245	68.6 (\pm 12.4)	46%	6 months, and annually	Spitzer QOL index	MMSE	β = 0.05 p = 0.04	20
Dhamoon, M.S US 2014	Randomised, controlled trial; Ischaemic stroke; Outpatient	2870	63.4 (\pm 10.7)	63%	9 months and annually for 5 years	SS-QOL	MMSE	β = 0.0086 p < 0.001	19
Fatoye, F.O Nigeria 2007	Case-control, cross- sectional; Unspecified;	109	60.7 (\pm 10.6)	59%	NR	WHOQOL- BREF	MMSE	NR	15

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
	Outpatient								
Franceschini, M Italy 2010	Longitudinal; Ischaemic and haemorrhagic; Rehabilitation facility	528	68.0 (\pm 11.9)	54%	2 and 12 months	EQ-5D	MMSE	β = 0.0009 p = 0.004	20
Gurcay, E Turkey 2009	Cross-sectional; Ischaemic and haemorrhagic; Rehabilitation facility	67	62.03 (\pm 13.2)	54%	3 months	SIS-16	MMSE	NR	20
Haacke, C Germany 2006	Cross-sectional; Ischaemic and haemorrhagic; Outpatient	77	71.7 (\pm 11.3)	45%	4 years	EQ-5D EQ VAS HUI2/3	MMSE	β = 0.016 (HUI2) β = 0.026 (HUI3) p <0.05	18

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Hilari, K UK 2010	Cross-sectional; Ischaemic and Haemorrhagic; Home	83	61.67 (\pm 15.5)	63%	3.5 years	SAQOL-39	Raven Coloured Progressive Matrices	$r = .27$ $p < .05$	21
Howitt, S.C Tanzania 2011	Case-control, cross- sectional; Unspecified; Outpatient	52	67.1 (\pm 13.9)	48%	3 years	WHOQOL- BREF	CSI-D	NS	22
Huang, Y Taiwan 2010	Randomised, controlled trial; Ischaemic and haemorrhagic; Rehabilitation facility	58	56.42 (\pm 11.7)	65%	18 months	SIS v3.0	MMSE	NS	20

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Jonkman, E.J Netherlands 1998	Case-control, longitudinal; Ischaemic; Hospital	35	55.3 (\pm 3.8)	71%	3, 6 and 12 months	SIP	WAIS-R WMS	NS	13
Kwa, V.I Netherlands 1996	Cross-sectional; Ischaemic; Home assessment	97	63.2 (\pm 14.6)	50%	2.3 years	VAS	CAMCOG	NS	19
Lee, A.C China 2009	Longitudinal; Ischaemic stroke; Outpatient	188	72.3 (\pm 9.4)	63%	1 and 6 months	Modified Rankin Scale for QOL	AMT	β = -0.114 p = 0.023	21
Mayer, S.A USA 2002	Cross-sectional; SAH; Telephone interview	113	49.4 (\pm 13.0)	32%	3 months	SIP	TICS	β = -0.320 p <0.001	21

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Meyer, B Germany 2010	Longitudinal; SAH; Outpatient	113	54.39 (\pm 14.1)	33%	Discharge, 6 and 12 months	EQ-5D	MMSE	NS	19
Nys, G.M.S 2005	Longitudinal; Ischaemic and haemorrhagic; Outpatient	91	61.6 (\pm 13.2)	52%	1 week and 7.5 months	SS-QOL	NPB	β = -0.261 p = 0.01	20
Park, J.H Korea 2013	Case-control, cross- sectional; Ischaemic and haemorrhagic; Outpatient	100	69 (\pm 7)	72%	3 months	EQ-5D	NPB	r = 0.29 p <0.05 (poststroke dementia) NS (poststroke cognitive impairment)	22

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Passier, P.E Netherlands 2012	Longitudinal; SAH; Outpatient	99	53.6 (\pm 12.2)	17%	3 and 12 months	SS-QOL	NPB	β = 0.40 p < 0.001	21
Peixoto, B Portugal 2017	Cross-sectional; Ischaemic and haemorrhagic; Outpatient	51	65.53 (\pm 13.6)	61%	11 months	ECVI-38 (Spanish version of SS- QOL)	MoCA	r = -0.479 p < 0.001	15
Rachpukdee S Thailand 2013	Longitudinal; Ischaemic and haemorrhagic; Hospital	125	61.8 (\pm 10.4)	61%	1 and 3 months	SF-36	CNS	OR = 5.72 p = 0.008 (1) OR = 3.17 p = 0.029 (3)	19

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Safaz, I Turkey 2016	Cross-sectional; Ischaemic and haemorrhagic; Rehabilitation facility	114	58.2 (\pm 14.2)	68%	NR	SS-QOL	MMSE	β = 0.047 p <0.001	15
Scott, R.B UK 2008	Randomised, controlled trial; SAH; Outpatient	573	NR	NR	12 months	FLP	NPB	NR	19
Springer, M.V USA 2009	Longitudinal; SAH; Telephone interview	232	52 (\pm 13)	29%	3 and 12 months	SIP	TICS	NR	22

Author, country and year	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Correlation (r), regression coefficient (β) or odds ratio (OR)	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Takemasa, S Japan 2016	Cross-sectional; Unspecified; Home assessment	17	76.3 (\pm 10.5)	47%	NR	Japanese Quality of Life Inventory for the Elderly with Dementia	NM Scale	$r=0.81$ $p < 0.01$	10
Taufique, Z 2016	Cross-sectional; SAH; Outpatient	1181	52.3	NR	1 year	SIP	NPB	OR = 8.4 (adjusted) $p < 0.001$	20
Van Wijk, I Netherlands 2007	Cross-sectional; TIA; Home assessment	190	72.5 (\pm 8.7)	67%	15.6 years	SF-36 EQ-5D	CAMCOG	NS	22

AMT- Abbreviated Mental Test; AQOL- Assessment of QOL scale; CAMCOG-Cambridge Cognitive Examination for the elderly; CNS- Canadian Neurological Scale; CSI-D- Community screening instrument for dementia; EQ-5D- EuroQOL-5D; EQ VAS- EuroQOL visual analogue scale; FLP- Functional Limitations Profile; HUI 2/3- Health Utility Index 2 and 3; MoCA- Montreal Cognitive Assessment; MMSE- Mini-Mental State Exam; NM scale- Nishimura's Mental State Scale for the Elderly; NPB- Neuropsychological battery; NR- Not reported; NS- Not significant; SAQOL-39- Stroke and Aphasia Quality of Life Scale-39; SF-36- Short Form- 36; SIP- Sickness Impact Profile; SIS- Stroke Impact Scale; SS-QOL- Stroke Specific-QOL; TICS- Telephone Interview for Cognitive Status; VAS- Visual analogue scale; WAIS-R- Weschler Adult Intelligence scale; WHOQOL-BREF- World Health Organization Quality of Life-BREF; WMS- Weschler Memory Scale

Table 6: Characteristics of studies measuring cognitive and/or HRQOL domains

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Barker-Collo, S New Zealand 2010	Longitudinal; Ischaemic and haemorrhagic; Home assessment	307	72.9 (\pm 11.1)	52%	5 years	SF-36	NPB	Only visual memory ($r = 0.163$) and language ($r = 0.121$) domains were significantly related to SF-36 mental component score in bivariate analysis.	22
Boosman, H Netherlands 2017	Longitudinal; Ischaemic and haemorrhagic; Rehabilitation facility	100	53.9 (\pm 13.4)	59%	50 days	SSQOL-12	Individual tests for attention, executive functioning and verbal memory	Attention, executive functioning, learning potential and verbal memory were not significantly associated with HRQOL.	21

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (± SD)	Males					
Bugge, C UK 2001	Longitudinal; Ischaemic and haemorrhagic; Home assessment	153	70.6	49%	1, 3 and 6 months	SF-36	MMSE	Self-perceived health status was not strongly related to cognitive function. However, significant associations were found between the following: -MMSE at 1 month and emotional role -MMSE at 3 months and general and mental health (MH) -MMSE at 6 months and MH and vitality One-month poststroke 30% (n=45) of stroke patients had abnormal cognitive function (MMSE <24).	19

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Carod-Artal, F.J Brazil 2009	Cross-sectional; Ischaemic and haemorrhagic; Rehabilitation facility	260	55.9 (\pm 14.5)	55%	21 months	SIS v3.0	MMSE	SIS communication (β = 0.36, p <0.001) and memory (β = 0.18, p <0.001) domains correlated with MMSE.	20
Chahal, N New Zealand 2011	Case-control, cross-sectional; SAH; Home assessment	27	62.22 (\pm 12.6)	44%	5 years	SF-36	NPB	Visual memory (r = 0.562*); Language (r = 0.549); Visuoperceptual (r = 0.462); Executive (r = 0.590*); Information processing (r = 0.584*) were all correlated with SF-36 (* p <0.01)	21
Clarke, P Canada 2002	Longitudinal;	282	75.9 (\pm 5.1)	46%	NR	Ryff measure	MMSE	Stroke survivors with lower scores on the MMSE reported a	21

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
	Ischaemic and haemorrhagic; Questionnaire					of psychological wellbeing		lower score on the 'sense of purpose in life' domain than those with higher cognitive function ($\beta = 0.07$; $p < 0.001$).	
Haug, T Norway 2010	Cross-sectional; SAH; Outpatient	26	49	23%	1 year	SF-36 GHQ-30	NPB	In patients with cognitive impairment, physical functioning ($p = 0.04$), role physical ($p = 0.004$) and general health ($p = 0.001$) domains of the SF-36 were significantly reduced compared to the means of the study population. Reduced scores on the GHQ-30 well-being domain ($p = 0.04$) were also found among	17

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
								the participants with poor cognitive functioning.	
Hochstenbach, J.B 2001	Longitudinal; Ischaemic and haemorrhagic; Outpatient	106	54.6 (\pm 11.3)	63%	72 days and 10 months	SIP	NPB	In univariate analysis, several cognitive tasks- mainly those that measured spatiotemporal and/or sequential aspects of behaviour- administered at 2 months poststroke were predictive of HRQOL at 10 months. Trail Making test (part B) emerged as an independent predictor of HRQOL in regression analysis (β = 1.048; p = 0.014).	22

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Huang, Y Taiwan 2013	Cross-sectional; Ischaemic and haemorrhagic; Rehabilitation facility	74	57.15 (\pm 11.7)	70%	19 months (mean)	SS-QOL	MMSE	Using the Chi-squared Automatic Interaction Detector method, MMSE was not a predictor of SS-QOL domain scores in the study sample.	18
Jeong, B.O Korea 2012	Longitudinal; Ischaemic; Hospital	422	64.5 (\pm 10)	58%	2 weeks	WHOQOL-BREF	MMSE	In the acute phase of stroke, impaired cognitive function was independently associated with lower HRQOL in three domains: physical factors (β = 0.44; p < 0.01), psychological factors (β = 0.42; p < 0.05) and environmental context (β = 0.33; p < 0.05).	19

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Jonsson, A.C Sweden 2005	Case-control, longitudinal; Ischaemic and haemorrhagic; Outpatient	274	74.3	56%	4 and 16 months	SF-36	MMSE	In stepwise linear regression, MMSE was associated with the Bodily Pain domain of the SF-36 only ($\beta = -.07$; $p = 0.050$).	20
Karmel, A Egypt 2010	Longitudinal; Ischaemic and haemorrhagic; Outpatient	50	55.3 (± 8.2)	62%	1 and 3 months	SIS 2.0	MMSE	MMSE score was strongly correlated with the memory ($r = 0.47$) and communication ($r = 0.43$) sub-scores on the SIS ($p < 0.001$).	18
Kauhanen, M.L Finland 2000	Longitudinal; Ischaemic and haemorrhagic; Outpatient	85	65 (± 12.5)	58%	3 and 12 months	SF-36	MMSE	No significant correlation between the RAND-36 sub-scales and MMSE scores was found.	20

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Kwok, T China 2006	Longitudinal; Ischaemic and haemorrhagic; Outpatient	247	70.5 (\pm 11.6)	50%	3, 6 and 12 months	WHOQOL-BREF	MMSE	In multilevel multivariate analysis, MMSE was not found to be a significant factor contributing to change in any of the HRQOL domain scores.	22
Larson, E.B USA 2003	Longitudinal; Ischaemic and haemorrhagic; Rehabilitation facility	34	65	41%	Admission to rehab and 6 months later	QOL battery	RBANS	Using inpatient RBANS visuospatial/ constructional, delayed memory, and attention Indexes, multiple regression predicted 46% of the variance in the cognitive Functional Independent Measure (FIM) at follow-up and 22% of the variance in motor FIM.	19

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Noble, AJ UK 2008	Longitudinal; SAH; Outpatient	94	53 (\pm 11)	43%	3 and 13 months	SF-36	MMSE	Cognitive disability did not make a significant contribution to the patient's mental or physical QOL (sub-scores of SF-36) in regression analysis. 33% of patients were classified as cognitive impaired at 3 months and 30% at 13 months.	19
Patel, M.D UK 2007	Longitudinal; Ischaemic and haemorrhagic; Outpatient	397	NR	53%	1 and 3 years	SF-36	MMSE	Cognitive impairment was an independent predictor for worse mental (β = -2.70) and physical (β = -3.04) health summary scores at 1 year and worse physical (β = -8.32) health summary scores at 3 years, on the SF-36.	17

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
Sarfo, F.S Ghana 2017	Case control, cross-sectional; Ischaemic and haemorrhagic; Outpatient	147	59.9 (\pm 13.7)	52%	3 months	HRQOLISP	MoCA V-NB	Health-related quality of life was lowest among poststroke dementia subjects, followed by vascular cognitive impairment without dementia and then stroke survivors without vascular cognitive impairment. This trend was most obvious in the psychosocial, cognitive, and eco-social domains of the HRQOLISP questionnaire but not in the physical domain. 73% of stroke participants demonstrated cognitive impairment on the MoCA (<23). 34% had vascular	21

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
								cognitive impairment without dementia and 14% had poststroke dementia.	
Verhoeven, C.L Netherlands 2011a	Cross-sectional; Ischaemic and haemorrhagic; Home assessment	92	63.7 (\pm 14.4)	49%	12 months	QOL domains: functional independence (BI); social participation (FAI); depressive mood (CES-D) and life	NPB	Impaired cognitive function correlated significantly with all QOL domains, most strongly with social participation and weakest with depressive mood ($r = 0.21$ (BI) $r = 0.63$ (FAI) $r = 0.31$ (LiSat-9) $p < 0.01$; $r = -0.24$ (CES-D) $p < 0.05$) In regression analysis, the predictive value of cognitive functioning diminishes after adjusting for demographic	19

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (± SD)	Males					
						satisfaction (LiSat-9)		characteristics and motor impairment. Regression analysis OR (without adjusting for confounders): 2.03 p<.01 (BI); 0.64 p<.01 (FAI); 0.31 p<.01 (LiSat-9)-0.24 (CES-D) p<.05	
Verhoeven, C.L. Netherlands 2011b	Longitudinal; Ischaemic and haemorrhagic; Outpatient	134	56.5 (±11.3)	59%	On admission to rehab and 1 and 3 years	Stroke-Adapted SIP	CAMCOG	In regression analysis, at one-year poststroke, perception ($\beta = -0.160$) was the cognitive variable most strongly correlated to health status. In addition, orientation was correlated with the total score ($\beta = -0.151$), physical domain ($\beta = -0.151$) and psychosocial domain ($\beta = -0.209$),	20

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
								and memory to the physical dimension ($\beta = 0.164$). At three years poststroke, perception ($\beta = -0.187$) was once again correlated with the SIP total score and physical dimension ($\beta = -0.180$), and language was correlated with the psychosocial dimension ($\beta = -0.149$).	
Vilkki, J Finland 2012	Longitudinal; SAH; Outpatient	101	48	50%	1 and 10 years after stroke	EQ-5D	NPB	Highly significant differences were found in the means of face recognition tests for patients with no problems on HRQOL vs those with problems ($p < 0.001$).	19

Author and country of research	Design, population and setting	Participants			Follow-up	HRQOL measure	Cognitive measure	Results	STROBE score
		No. of stroke patients	Mean age (\pm SD)	Males					
								This indicates that long-term outcomes are dependent on well preserved learning and memory functions.	
Van Zandvoort, M.J.E Netherlands 2005	Longitudinal; Ischaemic; Outpatient	27	56 (\pm 16)	54%	11 days and 21 months (mean)	SF-36 VAS	NPB	No significant relation was found between cognitive functioning and HRQOL by means of a linear regression conducted with different cognitive domain scores of the SF-36.	22

CAMCOG-Cambridge Cognitive Examination for the elderly; EQ-5D- EuroQOL-5D; GHQ-30- General Health Questionnaire; HRQOLISP- Health Related Quality of Life in Stroke Patients; MoCA- Montreal Cognitive Assessment; MMSE- Mini-Mental State Exam; NPB- Neuropsychological battery; NR- Not reported; RBANS- Repeatable Battery for Assessment of Neuro-psychological Symptoms; SF-36- Short Form-36; SIP- Sickness Impact Profile; SIS- Stroke Impact Scale; SS-QOL- Stroke Specific-QOL; VAS- Visual analogue scale; V-NP- Vascular Neurological Battery; WHOQOL-BREF- World Health Organization Quality of Life-BREF

3.3. Findings

3.3.1. Characteristics of included studies

Fifty-four studies have reported data on the association between cognitive impairment and health-related quality of life after stroke (13,217 patients [mean age 48-76]), with the number of participants ranging from 17 to 2870. Twenty-five longitudinal cohort studies; seventeen cross-sectional; seven case-control; and five randomised controlled trials were included in this review. Of these studies, nine included ischaemic strokes only; ten studied subarachnoid haemorrhage; one focused on patients who had a TIA or minor stroke; and three were unspecified. The remaining 31 studies included both ischaemic and haemorrhagic stroke participants however, data could not be extracted on the stroke subtypes. To date, no studies assessing the relationship between cognitive impairment and HRQOL have been conducted within a dedicated intracerebral haemorrhage cohort. The relevance of this is that the results of the studies in this review may not be generalisable to ICH, the least treatable and most disabling type of stroke.

Follow-up time of included studies varied significantly, from 1 week to 15 years after stroke onset. The settings for these studies also differed at follow-up: three were hospital based; 10 were conducted in the patient's home; 10 within rehabilitation centres; 27 were based in outpatient departments; 3 were conducted over the telephone; and one was assessed through a community questionnaire.

Results are also difficult to compare due to the different cognitive assessment strategies that were employed. Whilst the majority utilised general screening measures such as the MMSE, MOCA or TICS to assess for cognitive impairment, sixteen studies used comprehensive neuropsychological test batteries and assessments. A variety of measures were also used to assess HRQOL outcomes, from a simple unidimensional visual analogue scale, to generic measures of health-related quality of life such as the EuroQOL-5D (EQ-5D), to more in-depth and stroke specific assessments such as the Stroke Specific Quality of Life scale (SS-QOL). It is also worth noting that some of the HRQOL scales included specific items on cognition (i.e. SS-QOL and Stroke Impact Scale (SIS)), making the associations seem somewhat circular (Cumming et al, 2014).

Of the 32 studies that assessed global cognition against total score on the HRQOL measure, 25 revealed significant relationships between cognitive impairment and health-related quality of life. In addition to this, a further four studies revealed significant associations between measures of individual cognitive domains and overall HRQOL.

3.3.2. Studies showing an association between global cognitive impairment and HRQOL

A significant association between global cognitive impairment and HRQOL was reported by 25 studies in this review. While some studies only measured bivariate relationships (Adamit et al, 2015; Alvarez-Sabin et al, 2016; Ankolekar et al, 2014; Canuto, Nogueira and de Araujo 2016; Park et al, 2013; Scott et al, 2008; Springer et al, 2009; Takemasa et al 2016), those using multivariate analysis often found that the significant relationships in bivariate analysis were no longer significant in regression analysis (Fatoye et al, 2007; Gurcay et al, 2009; Hilari et al 2010; Peixoto et al, 2017). An example of this was the study by Hilari et al (2010) which was one of the first to specifically look at the HRQOL of people living with aphasia. Eighty-three participants with chronic aphasia were assessed at a mean time of 3.5 years after their stroke. Although HRQOL was significantly poorer in participants with lower cognitive levels, in the regression model, emotional distress, involvement in home and outdoor activities, extent of communication disability and number of comorbid conditions explained 52% of the variance.

Several studies found significant associations between cognitive impairment and lower HRQOL in the first 3-9 months after stroke onset (Adamit et al, 2015; Ankolekar et al, 2014; Chen-Min et al, 2015; Dhamoon et al, 2010; Dhamoon et al, 2014; Mayer et al, 2002; Nys et al, 2007; Park et al, 2013; Rachpukdee et al, 2013; Gurcay et al, 2009). One of the largest studies of cognition after acute stroke was a randomised controlled trial assessing the management of blood pressure in previously independent ischaemic and haemorrhagic patients (Ankolekar et al, 2014). 1572 participants were assessed over the telephone 3 months after stroke onset with modified versions of the MMSE and TICS. By 90 days, cognitive impairment was present in 38% of participants, where both measures of cognition were significantly related to reduced health-related quality of life on the EQ-5D. Although the multiple exclusion criteria of the randomised controlled trial will have limited eligibility, patients were enrolled from 18 different countries, across 5 continents, giving it great external validity and generalisability. Similar results were obtained by Adamit et al (2015),

who assessed 249 participants with mild ischaemic strokes in their homes at 3 months post-event. Despite being able to perform basic activities of daily living independently, 67% of patients scored less than 26 on the MOCA, indicating possible cognitive decline. In addition, there were significant correlations between lower scores on the MOCA and most domains on the Stroke Impact Scale (a stroke-specific, self-report, health status measure). Patients suffering from mild strokes may often be overlooked by health care systems and rehabilitations programmes as they are likely to be functionally independent. Given that two-thirds of participants had some level of cognitive dysfunction, this study emphasises the necessity of follow-up. A major strength of this study was that participants were evaluated at home, in their natural environment.

Four studies indicated that cognitive impairment in the first 1-3 months after stroke was an independent predictor for lower HRQOL at 6-12 months (Cumming et al, 2014; Lee et al, 2009; Nys et al, 2007; Passier et al, 2012). In the first of these studies, Nys et al (2007) concluded that cognitive impairment in the early phase of stroke (first month) is an independent risk factor for reduced health-related quality of life after 6 months. As well as long-term depressive symptoms being independently predicted by cognitive impairment at baseline, patients with cognitive impairment demonstrated lower HRQOL scores at 6 months poststroke than those without. Despite participants having a high level of cognitive function, in stepwise regression analysis Lee et al (2009) found that cognitive scores at one month could predict HRQOL at 6 months. Although HRQOL was measured using a single item tool, the results suggest that clinicians need to observe for early signs of mild cognitive impairment to enhance poststroke quality of life. In addition, among stroke patients who were living at home, Passier et al (2012) and Cumming et al (2014) both showed that cognitive functioning at 3 months was an important predictor of HRQOL at 1 year.

Five studies assessed patients at 12 months after their stroke and found associations between lower cognitive scores and lower global HRQOL. Of these, two studies recruited patients who had either an ischaemic and haemorrhagic stroke (Franceschini et al, 2010; Peixoto et al, 2017), and three recruited SAH patients (Scott et al, 2008; Springer et al, 2009; Taufique et al, 2016). In addition, a further four studies evaluated the longer-term effects (2-4 years) of an ischaemic or haemorrhagic stroke (Alvarez-Sabin et al, 2016; Haacke et al, 2006; Hilari et al, 2010; Safaz et al, 2016). In a randomised controlled trial assessing the effect of citicoline treatment on health-related quality of life and cognitive performance in patients

with a first ischemic stroke, global cognitive impairment was associated with poorer HRQOL at 2 years (0.55 vs 0.66 in utility; $p = 0.015$; where 1 represents the patient without any health problems and 0 the worst health status) (Alvarez-Sabin et al, 2016). Twenty-three percent of patients were classified within the group with poor or very poor quality of life (utility < 0.5) however, patients treated with the study drug had less cognitive impairment at 2 years (28% v 39%).

Conclusion: Twenty-five studies reported a significant association between global cognitive impairment and HRQOL. While most studies only measured bivariate relationships, those using multivariate analysis often found that the significant relationships in bivariate analysis were no longer significant in regression analysis. Ten studies found significant associations between cognitive impairment and lower HRQOL in the first 3-9 months after stroke onset, and a further four studies indicated that cognitive impairment in the first 1-3 months after stroke was an independent predictor for lower HRQOL at 6-12 months. In addition, nine studies assessed patients 1-4 years after their stroke and found associations between lower cognitive scores and lower global HRQOL. These results suggest that health-related quality of life is consistently impaired in patients suffering from cognitive impairment after stroke and that it is a problem that begins early after stroke onset and continues to be present in the long-term.

3.3.3. Studies showing no association between global cognitive impairment and HRQOL

Only seven studies did not find a significant impact of cognitive impairment on patient's health-related quality of life (Chou 2015; Howitt et al, 2011; Huang et al, 2010; Jonkman, Weerd and Vrijens 1998; Kwa, Limburg and Hann 1996; Meyer et al, 2010; van Wijk et al, 2007). Kwa, Limburg and Hann (1996) conducted the first study to specifically examine the influence of cognition on the health-related quality of life in 129 patients, two years after their ischaemic stroke. Cognitive function was assessed with the Cambridge Cognitive Examination for the elderly (CAMCOG- a concise neuropsychological test for the assessment of cognitive impairment in elderly people) and HRQOL with a visual analogue scale. In multivariate analysis, cognitive function was not found to be significantly associated with health-related quality of life. However, it should be noted that the patient sample was

restricted to a relatively well group of stroke survivors, making the results less transferable to the wider stroke population. In a similar study investigating long-term health-related quality of life of patients in Tanzania, Howitt et al (2011) assessed patients 1-5 years (mean 3 years) after their incident stroke. Lower levels of health-related quality of life were associated with depression, reduced social interaction and physical disability and motor function. Although cognitive function played less of a role than motor function in predicting health-related quality of life, findings could be related to the inability of those with significant cognitive impairment to provide accurate information. In addition, many of the participants struggled to rate their emotions and health status on a rating scale.

Another study worth noting is that conducted by Jonkman, Weerd and Vrijens (1998), who evaluated the different factors which were deemed to be important for health-related quality of life in the 3-12 months following an ischaemic stroke. Health-related quality of life scores, as measured by the Sickness Impact Profile (SIP- assesses quality of life in patients who have sustained a stroke), improved in the 3-12 months after the stroke but were not correlated with cognitive disturbances in regression analysis. The sample was confined to a relatively young group of stroke survivors (aged between 25 and 70 years), none of which returned to their original occupational level. As a result, the authors have suggested that the patients may have been less confronted by their decrease in cognitive abilities than if they had returned to their previous occupational capacity.

Conclusion: Although seven studies did not find a significant impact of cognitive impairment on patient's HRQOL, some of these studies were confined to a younger and relatively well group of stroke survivors.

3.3.4. Studies showing an association between individual cognitive domains and overall HRQOL

From the 22 studies that investigated cognitive/HRQOL domains (as measured by standardised assessment tools or tests batteries), only four revealed a significant association between individual cognitive domains and overall HRQOL (Chahal, Barker-Collo and Feigin 2011; Hochstenbach et al, 2001; Verhoeven et al, 2011a; Vilkki et al, 2012).

In a selective sample of 106 patients who were all younger than 70 at stroke-onset and lived at home, Hochstenbach et al (2001) were the first researchers to show that several cognitive tasks- mostly in the attention domain- administered at 2 months poststroke, were predictive of health-related quality of life at 10 months. However, some of the significant univariate relationships were no longer significant in regression analyses. Multivariate analysis showed that poor health-related quality of life was more likely if patients had a poor result on the Trail Making Test (TMT) Part B (requiring speed of processing and visual scanning). A possible explanation for these results is that poor performance on the TMT Part B is an indication of difficulty in performing under time pressures, as well as being able to adequately shift mental states. The authors argued that these abilities are crucial to performing many daily life activities such as preparing dinner, going shopping, doing housework etc.

In accordance with these results, Nys et al (2007) concluded that among all cognitive disorders, visual perceptual/construction ability was the cognitive domain with the strongest link to health-related quality of life. Likewise, in addition to visual memory and language, Chahal, Barker-Collo and Feigin (2011) found that impairments in visual perceptual ability, executive functioning and speed of information processing impacted long-term (5 years poststroke) functional outcomes and HRQOL of SAH survivors. In regression analysis at one- and three-years poststroke, CAMCOG scores were significant predictors of long-term health status in patients with stroke (Verhoeven et al, 2011a). As before, visual perception was the cognitive variable most strongly correlated to HRQOL. All these studies gave some indication that executive function and visuospatial ability are closely related to HRQOL after stroke. Because the tasks used to assess these abilities are typically speed-dependent, these results may therefore be mediated by a more generalised speed of processing capability.

In light of this research, Cumming et al (2014) aimed to assess whether speed of processing in the acute stage after stroke onset would be independently related to HRQOL at 12 months. In addition to their finding that cognitive impairment at 3 months poststroke was associated with lower HRQOL at 12 months (even when covariates were taken into account), poorer attention and visuospatial ability were significantly and independently related to lower long-term HRQOL. Of those participants that were tested acutely (n=33), the researchers found that faster choice reaction times at 2 weeks poststroke was significantly associated with better HRQOL at 12 months, suggesting that straightforward speed of processing tasks (such as the Trail Making B) may be more sensitive to the extent of brain damage than other

neuropsychological tasks. However, the sample was made up of mild and moderate stroke patients and is therefore not generalisable to more severely impaired stroke survivors.

In contrast to these results, Vilkki et al (2012) found that of all cognitive domains tested 1 year after SAH, the only predictive variable for HRQOL 11 years after stroke was the face recognition test. This indicates that long-term outcomes are dependent on well preserved learning and memory functions.

Conclusion: From the 22 studies that investigated cognitive/HRQOL domains, only four revealed a significant association between individual cognitive domains and overall HRQOL. From these studies, executive functioning, speed of information processing and visual perception were found to be the cognitive domains most closely related to HRQOL after stroke

3.4. Discussion

Health-related quality of life is the closest thing we have to a central and universally important health outcome measure. Fifty-four published studies were reviewed in which the effect of cognitive impairment on health-related quality of life was explored after stroke. The results of the previous studies are difficult to compare. The assessment of cognitive impairment ranged from general screening measures such as the MMSE, to the use of a full and comprehensive neuropsychological test battery covering various cognitive domains. In addition, the researchers used a variety of measures to assess health-related quality of life, where assessments took place between one week and 15 years after stroke onset.

Despite these methodological challenges, previous research indicates that cognitive impairment after stroke can have profound consequences to the patient's health-related quality of life. Of the 32 studies that assessed global cognitive impairment against overall HRQOL, 25 showed a significant association. The available evidence suggests that health-related quality of life is consistently impaired in patients suffering from a cognitive dysfunction and that it is a problem that begins early after stroke onset and continues to be present in the long-term. From the studies which investigated cognitive/HRQOL domains, executive functioning (particularly speed of information processing and attention) and visuospatial ability were found to be closely related to HRQOL after stroke.

This literature review benefited from thorough ascertainment of a large number of relevant studies, using multiple electronic databases, in an attempt to be comprehensive and avoid reporting bias. The use of a broad review question has the advantage that the findings are applicable to a wider range of settings and populations, with less opportunity for chance findings (Pollock and Berge 2018). Studies underwent a comprehensive critical appraisal and judgement relating to whether there were any potential risks of bias within the study. The average methodological quality score was 19, with most studies attaining a methodological score of between 19 and 22, suggesting that the quality of included studies was at a high standard.

Although the literature indicates that a relationship exists, the exact nature of the relationship remains unclear. Cognitive impairment and health-related quality of life are complex issues that have multiple interacting determinants. There is more to health-related quality of life than someone's cognitive ability or neurological impairment. To explore the relationship between objective (i.e. MOCA) and subjective measures (i.e. EuroQOL-5D), and to identify other potential factors that may be closely linked to someone's HRQOL, mixed method studies are required. Not only would this add to the existing understanding of the impact and meaning of stroke, qualitative interviews would allow us to further understand how stroke patients adjust and adapt to their situation. Whilst there have been several qualitative studies on quality of life after stroke, none of these focussed on patients with cognitive impairment. In addition, no quantitative studies have examined cognition and its resultant impact on health-related quality of life within a dedicated ICH cohort. This research is important as it may contribute to rehabilitation in terms of raising awareness and educating professionals, family members and carers on the long-term consequences of ICH and how it may affect aspects of a patient's health-related quality of life and functional outcome.

4. Research design

This chapter begins by setting out the aims of the research. To help orientate the reader, an overview of the different studies that are components of this research has been provided. The chapter will then go on to explain the research design that has been adopted; this involves an examination of the theoretical underpinnings of the methodology, as well as an explanation of why this design was deemed most suitable for meeting the research aims. The chapter concludes with an exploration of ethical considerations and details on patient involvement in the research process.

4.1. Research aim and objectives

The overall aim of this research study is to explore the outcomes and experiences of people living with cognitive impairment and intracerebral haemorrhage.

To meet this aim, three research objectives were developed. These are:

- a) To study the prevalence of pre-existing dementia and cognitive impairment in patients with ICH, and to quantify their incidence at specific time points thereafter,
- b) To investigate the demographic, clinical, radiographic and functional outcomes associated with the occurrence of cognitive impairment following an ICH, and
- c) Evaluate the experience of life after ICH with cognitive impairment.

4.2. Orientation to research studies linked to this thesis

4.2.1. *LATCH*

The Lothian Audit of the Treatment of Cerebral Haemorrhage (LATCH) identified all residents in the Lothian Health board region of Scotland, who were aged ≥ 16 years at the time they were diagnosed, with first-ever or recurrent ICH. Adults with exclusively extra-axial intracranial haemorrhage (haemorrhages that are external to the brain parenchyma) or ICH definitely attributable to trauma or haemorrhagic transformation of an ischaemic stroke were excluded.

Incident ICH cases were identified using multiple overlapping sources of case ascertainment (full details of which have been provided by Samaresekera et al, 2015). The NHS Lothian Caldicott Guardian approved the use and transfer of patient identifiable information for LATCH. Patients in NHS Lothian were informed about the use of their data for audit, and information leaflets about LATCH were distributed to inform patients and their carers about their right to opt out. The team collected data on demographics, medical history, and medication use at time of ICH diagnosis by interviewing patients, their families or carers at the time of presentation and reviewing primary care and hospital records.

Using the LATCH database, I carried out a retrospective analysis (henceforth referred to as LATCH COG) of all patients diagnosed with ICH in the Lothian region between June 2010 and May 2013 inclusive, with available CT data (n=404). Analyses of an anonymised dataset, extracted from the audit database held on NHS and University servers, did not require NHS ethics approval. The primary aim of this analysis was to give a crude measure of the prevalence of dementia and cognitive decline before an ICH and quantify their incidence at specific time points thereafter (research objective (a)).

4.2.2. LINCHPIN

Patients with ICH who were identified by LATCH had the opportunity to participate in the Lothian IntraCerebral Hemorrhage, Pathology, Imaging and Neurological Outcome (LINCHPIN) study. This was my supervisor's (Professor Rustam Al-Shahi Salman) prospective community-based research study examining the causes of ICH using clinical assessments, brain MRI, blood samples and research autopsy in case of death. The Scotland A Research Ethics Committee (10/MRE00/23) approved LINCHPIN. Written informed consent was obtained by the Chief Investigator or Senior Research Nurse from all participants, or their nearest relative when participants did not have mental capacity. Data collection started on 1st June 2010 and ended on 31st December 2016.

At the time that I was conducting my PhD, the LINCHPIN research team was primarily made up of four members, two of which were my supervisors: Chief Investigator (Professor Rustam Al-Shahi Salman), Senior Research Nurse (Christine Lerpiniere), Project Co-ordinator and an IT Programmer.

4.2.3. LINCHPIN COG

LINCHPIN COG is a prospective, observational cohort sub-study of cognitive impairment in patients who had an intracerebral haemorrhage. Six-month survivors of ICH who had already consented to participate in the LINCHPIN study were given the opportunity to take part in a more detailed assessment of their cognition and quality of life at six months and 1-2 years following their ICH. The sub-study was approved by the Scotland A Research Ethics Committee on the 6th March 2015 in the form of a substantial amendment (Appendix 5). NHS Lothian Research and Development approval was then awarded on the 12th March 2015 (Appendix 6).

Data collection for LINCHPIN COG started in March 2015 and was completed in February 2018. In order to avoid selection bias, I aimed to consecutively assess all patients who survived to 6 months that had consented to LINCHPIN. This sometimes meant visiting patients in nursing homes or on a hospital ward, with the family's consent. For patients who were unable to be cognitively assessed, for example as a result of severe aphasia, visual impairment or neurological impairment, I relied on those tools that could be completed by the caregiver or family member. Analysis was carried out to investigate the frequency of cognitive impairment before and after ICH and any clinical, demographic, radiographic or functional outcome associations with its occurrence (research objective (b)).

4.2.4. Qualitative interviews

To help further understand the different ways in which cognitive impairment can impact a person's life following an ICH, semi-structured qualitative interviews were conducted with six LINCHPIN COG participants with varying levels of cognitive decline at 6-24 months after their ICH. During these interviews, the participants discussed how they and their family members had been able to adjust and adapt to the long-term consequences of their ICH (research objective (c)).

4.3. Study setting

For all studies mentioned above, patients were included if they were resident in the region served by the NHS Lothian Health Board. The region has three main hospitals (Royal Infirmary of Edinburgh, Western General Hospital and St John's Hospital), all of which have a specialist stroke unit.

4.4. Design

When designing a research study, there are numerous approaches to choose from. When seeking to understand the experiences of people living with cognitive impairment after a chronic disabling condition like ICH, although a purely quantitative or qualitative approach to the research could have been taken, mixing methods was likely to provide me with the most comprehensive picture. While many of the quantitative studies on stroke have relied on objective measures of functional outcome and health-related quality of life, qualitative research has focused on the complexities of how participants make sense of their experience (Clarke 2009). As such, quantitative results can tell us how many patients experience cognitive impairment and decreased HRQOL after their ICH, whereas qualitative findings can help shed light on the underlying process by which health-related quality of life is maintained in some patients and lost in others. Both approaches can be seen to make separate, yet equally important, contributions to our understanding of the stroke experience.

4.4.1. Mixed Methodology

The use of both qualitative and quantitative approaches in a single study has been the subject of considerable controversy and remains a relatively uncommon practice in the study of health and illness (Creswell 2011). The underlying problem when trying to combine these two strategies comes from the conflicts of different paradigms. Some authors believe that paradigms have rigid boundaries that cannot be mixed, and that the applications of qualitative and quantitative methods rely on a different set of assumptions about the world and the ways of learning about it (Johnson and Onwuegbuzie 2004). Whilst quantitative research falls within the positivist paradigm (which assumes that the world is stable and

predictable, with a single reality), qualitative research is thought to fall within the constructivist paradigm (which assumes that the world is made up of multiple socially constructed realities that need to be interpreted). However, a growing number of academics advocate for the mixing of methods and maintain that:

“both views of the nature of reality are compatible and essential to understand the human experience” (Haase and Myers 1988, p.132; Morgan 1998).

This aligns with my own perspective that reality is something that can be measured and generalised yet is unique to everyone.

For the purposes of this thesis, the definition of mixed methods that has been chosen is from Creswell and Clark (2007, p.5):

“Mixed methods research is a research design with philosophical assumptions as well as methods of inquiry. As a methodology, it involves philosophical assumptions that guide the direction of the collection and analysis... As a method, it focuses on collecting, analysing, and mixing both quantitative and qualitative data in a single study... Its central premise is that the use of qualitative and quantitative approaches, in combination, provides a better understanding of research problems than either approach alone.”

4.4.2. Theoretical underpinnings

When designing a study, it is important for the researcher to think about their philosophical assumptions and how these might guide inquiry and fit into the methods of their research. Researchers bring a worldview to their study (also referred to as paradigm) that is composed of beliefs and assumptions about the nature of knowledge and provides a guide that can be used to ground their research (Creswell and Clark 2011). The choice of research questions and methods is therefore a reflection of the researcher’s philosophical understanding of the world, even if it is not made explicit.

Pragmatism, a worldview which is often associated with mixed methods, focuses on the problem to be researched and provides a basis for a position that has been stated as the *“dictatorship of the research question”* (Tashakkori and Teddlie 2010, p.21). Pragmatic

researchers believe that it is the research question that should drive the design and methods of a study and reject the forced choice between traditional constructivist and positivist ways of knowing in order to look at what is meaningful from both (Biesta 2010). A similar argument was made by Howe (1988) who suggested that researchers should “*forge ahead with ‘what works’*” (p. 15). Rather than using metaphysical concepts such as ‘truth’ and ‘reality’, pragmatism accepts that there are both singular and multiple realities that are open to inquiry and orientates itself to solving practical problems in the real world (Biesta 2010). As stated by Casebeer and Verhoef (1997), we should view:

“qualitative and quantitative methods as part of a continuum of research techniques, all of which are appropriate depending on the research objective” (p.132).

Pragmatic researchers see the value of mixing methods as it extends our understanding of a phenomenon using multiple perspectives. This emphasis also points to the underlying belief in complementarity research that qualitative and quantitative approaches can be combined to ‘compliment’ the advantages and disadvantages present within each (Shannon-Baker 2015).

4.4.3. Complementarity

A mixed methods approach has been chosen for its complimentary abilities (Greene, Caracelli and Graham 1989). The key goal for studies seeking complementarity is to:

“measure overlapping but also different facets of a phenomenon, yielding an enriched, elaborated understanding of the phenomenon” (Greene, Caracelli and Graham 1989, p.258)

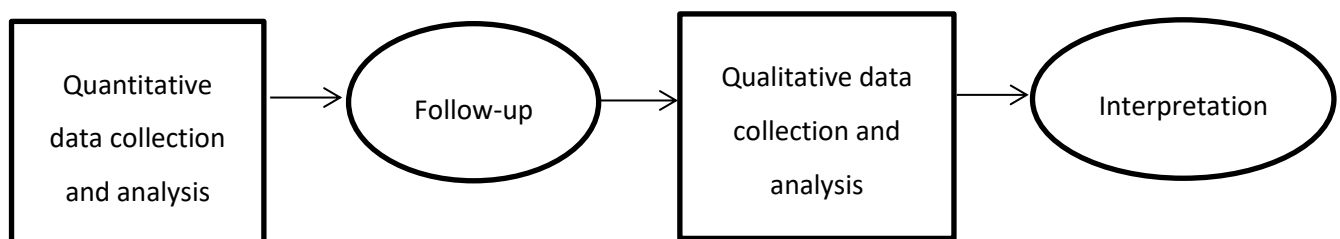
Complementarity refers to enhancement or clarification, where the quantitative and qualitative substudies represent different pieces of the puzzle. By undertaking qualitative interviews, I hoped to illustrate and explain the results of the quantitative assessments by allowing the participants to elaborate on their experiences in their own words. As stated by Creswell and Clark (2011, p. 63), adding a qualitative element allows researchers to “*put meat on the bones of dry quantitative findings*”. Mixing methods avoids the limitations of a single

approach and allows the researcher to use the methodological tools that are best suited to addressing the research questions. By approaching the study of cognitive impairment and ICH from both philosophical perspectives, a greater depth of knowledge can be obtained about the stroke experience.

4.4.4. Explanatory sequential design

Although there are many options when designing a mixed methods study in terms of the timing and priority given to the two different strands of inquiry, I decided to choose an explanatory sequential design. Using this design, the researcher starts with the collection and analysis of quantitative data, which has the priority for addressing the research questions. This is then followed by the subsequent collection and analysis of qualitative data. The researcher then interprets how the qualitative results help to explain the initial quantitative findings (see Figure 4). As is the case for the present study, this design can be used when the researcher wants to use quantitative results about participant characteristics to guide purposeful sampling for a qualitative phase (Tashakkori and Teddlie 1998). The straightforward nature of this design allows the study to be reported in distinct phases, a quantitative section followed by a qualitative section, with a final discussion that brings the results together (Creswell et al, 2003).

Figure 4: Explanatory sequential design



4.5. Ethical considerations

Conducting research with stroke survivors is surrounded by a multitude of ethical quandaries, each of which will be discussed separately below:

- Inclusion of adults without mental capacity
- Assessment of mental capacity
- Consent from adults without mental capacity
- Withdrawal of consent
- Inclusion of adults with aphasia
- Interviewing participants who are cognitively impaired
- Potential distress to participants
- Duration of interview
- Confidentiality
- Data protection
- Possible risk to me as a researcher

The majority of the ethical considerations discussed apply to LINCHPIN COG however, issues around confidentiality and data protection also apply to LATCH COG.

4.5.1. Inclusion of adults without mental capacity

Due to the nature of LINCHPIN COG, it involved the recruitment of some participants who did not have the mental capacity to give informed consent. It was felt that the inclusion of adults who were unable to consent for themselves was important for a number of reasons. Firstly, this group have been poorly represented in previous studies of cognition after ICH. The study would also be extremely biased if I excluded adults with incapacity and I would underestimate the frequency of cognitive impairment and dementia. Most importantly however, I wanted the results of the study to be generalisable to the entire population of patients with intracerebral haemorrhage.

In order to protect individuals from any harm, the following steps were taken when recruiting adults who lacked the capacity to consent:

- Because of the vulnerability of adults without mental capacity, I had a discussion with the participant's nearest relative (with the support of the Senior Research Nurse) to assess their suitability to take part in the research, before the decision to consent was made. It was made explicit that relatives had the right to withdraw the participant from the study at any time, without the care of their relative being affected.
- My view of consent was not as the result of a single interview but as an ongoing process. I encouraged relatives to discuss participation with other family members before reaching a decision.
- The consent process was tailored to each individual participant. Provision was made for the participant potentially regaining capacity, in which case he/she was then asked whether they wished to continue participating in the study.

In patients who were so mentally incapacitated that they could not complete any of the quantitative assessments of cognitive function, only the National Institutes of Health Stroke Scale was carried out with the participant to assess the level of physical impairment. Their relative was then asked to fill out two questionnaires on the participant's behalf.

4.5.2. Assessment of mental capacity

Capacity to consent to research participation differs from capacity to consent to treatment. In order to decide whether an individual had capacity to make a decision, I needed to consider whether:

1. The person had a mental disorder (which includes mental illness, learning disability, dementia and acquired brain injury), or severe communication difficulty because of a physical disability (such as stroke or severe sensory impairment)? And, if so,
2. Had it made the person unable to make the decision or decisions in hand?

For the purposes of the Adults with Incapacity (Scotland) Act 2000, to prove that a participant had mental capacity I needed to show that the individual had the capacity to consent to participation in the research at the time that the consent was required to be made. In order to show that an individual had the mental capacity to consent, I needed to prove that the participant could (British Medical Association 2016):

1. Understand information- did the participant understand what the research was about?
2. Retain information- could the person hold the information in their mind long enough to use it to make a decision?
3. Use or weigh up the information
4. Communicate their decision

If the answer was no to elements one to three then, on the balance of probabilities, the participant was deemed to be unable to reach a decision themselves.

4.5.3. Consent from adults without mental capacity

Mental incapacity is an inability to comprehend and retain information necessary to make the decision, and/or an inability to weigh up the information in the process of making the decision (Mental Capacity Act 2005). Participants who were unable to consent were likely to be those admitted with intracerebral haemorrhage causing an impairment of consciousness or language. Potential participants who were unable to give informed consent were enrolled into LINCHPIN COG if their proxy (usually the nearest relative) provided consent (see Box 9 for the Mental Health Act 1983 definition of relative).

Box 9: Mental Health Act 1983 definition of relative

The Mental Health Act 1983 defines the term relative as any of the following persons:

- (a) husband or wife (or civil partner)
- (b) son or daughter;
- (c) father or mother;
- (d) brother or sister;
- (e) grandparent;
- (f) grandchild;
- (g) uncle or aunt;
- (h) nephew or niece.

The general rule is that the nearest relative is the person who comes highest on the list.

Nearest relatives were asked to consider any previous wishes that the participant may have verbally or otherwise expressed about their participation in research. I was guided in the timing of consent by the participant, their relatives and the clinical situation, and encouraged relatives to discuss participation with other family members before reaching a decision.

Although some of the participants were cognitively impaired, an inability to consent was not assumed. If an individual was cognitively impaired, I worked alongside the participant, respecting those areas of functioning where the participant had retained competency. By viewing consent as an ongoing process, I re-checked the participant's willingness to remain involved in the study, particularly where consent had been taken two weeks prior to assessment.

Participants who initially lacked the capacity to consent but later regained it had the opportunity to provide consent themselves, overriding any wishes previously expressed by their representative. In such an event I provided information about the study and sought their consent at an appropriate time, ensuring that a member of their family was present where possible.

4.5.4. Withdrawal of consent

Participants were withdrawn if:

- Having consented to participate in the study, the participant changed their mind and no longer wished to participate.
- Where participants lacked the capacity to consent to entering the study and consent had been given by their nearest relative, they could be withdrawn if the person who had given consent changed their mind and no longer wanted them to take part in the study.
- A participant having been entered into the study with consent given by their nearest relative, on regaining capacity, no longer wished to participate.

4.5.5. Inclusion of adults with aphasia

Stroke often results in impairment in expressive language. Previous studies on stroke related cognitive impairment tended to use specific inclusion criteria where patients with aphasia were often excluded (Pendlebury and Rothwell 2009). Exclusion of those participants with aphasia is often undertaken due to the methodological issues encountered when trying to assess cognition in such patients (Pendlebury et al, 2015). However, excluding participants with aphasia limits the generalisability of findings. To ensure that findings were applicable to the wider ICH population, I endeavoured to include patients with expressive language impairments. Due to the inherent difficulties of assessing capacity in patients with communication difficulties, written consent was taken from the participant's nearest relative.

Where possible, the same assessment tools were used as for those without aphasia. When conducting the qualitative interviews, adjustments were made to accommodate language difficulties depending on the needs of the participant. Adjustments included the option of having a close family member present for support and to help with clarification, providing extra time for responses and additional breaks as necessary.

4.5.6. Interviewing participants who are cognitively impaired

Although interviewing those who are cognitively impaired can be challenging at times, such individuals have important views and perspectives that should not be excluded (Lloyd, Gatherer and Kalsy 2006). Qualitative research requires effective communication to optimise participant responses. One strategy for this is to conduct interviews in a place that is familiar and comfortable, for example the participant's home. I also ensured that interview questions were structured using terminology that was understandable to the participant, allowing ample time for responses (Beuscher and Grando 2009).

4.5.7. Potential distress to participants

It was predicted that the qualitative interview may have elicited upsetting memories for some participants as they recalled their experiences and the impact the stroke had on their lives. In addition, some of the quantitative questionnaires asked questions about mood, anxiety and depression. It was acknowledged that this may cause distress and participants were informed that they did not have to complete the questionnaires if they found them upsetting.

On the few occasions where participants became upset, I managed participant distress firstly by reassuring the participant and acknowledging that they were upset (e.g. 'Are you okay', 'Would you like to stop the interview for a while?'), and then by talking through whatever it was that had caused them to become distressed. In all cases, participants were happy to continue with the interviews or questionnaires after pausing for a short time.

The cognitive and functional assessments were also identified as having the potential to lead to distress for stroke participants, particularly where they lacked insight into the extent of their impairments. Participants were offered a short break if required and were given the option to discontinue whatever research activity was being performed at the time.

Consent was sought from all participants to contact their GP with a summary of the cognitive and functional outcome assessments. If it became apparent during any of the study visits that a patient was suffering from mental health issues or expressed suicidal thoughts, this was highlighted in the letter to the GP.

4.5.8. Duration of interview

Both the quantitative and qualitative interviews were expected to take between 60-90 minutes each. Stroke survivors often experience fatigue and it was possible that some of the participants would find this a long time to concentrate. Participants were given the choice of setting for the interview – in their own home or in a clinic setting, to make them most comfortable. Participants were also made aware that they could stop testing for breaks or could complete the assessments over two appointments.

4.5.9. Confidentiality

As part of this study, patients gave consent for the LATCH/LINCHPIN research team to access their identifiable data. The identifiable information was processed by the research team which included medical, computing and administrative staff, all of whom had a duty of confidentiality to the participants and were either NHS employees or had NHS honorary contracts.

Only appropriately trained and authorised members of the research team had access to participants' personal data during the study. The consent form specified that any information collected would be kept confidential by the University of Edinburgh research team and only made available to other researchers in a form which preserved anonymity.

Audio recordings of the qualitative interviews were made on an encrypted digital dictaphone and downloaded onto the secure NHS server. These files were password protected and labelled with a participant number. Once downloaded, original recordings were deleted from the dictaphone.

To ensure anonymity and confidentiality of personal data, transcripts were given a participant number and did not contain names or contact details. Due to the nature of this research, direct quotations have been used in the dissemination of the findings. A sufficient degree of anonymity has been ensured by removing all obvious descriptors and identifiable information from the extracts used. When anonymising data, I was sensitive to changing anything that might have been considered identifiable without detracting from the richness of the content or changing it so much that it altered the meaning substantially (Guenther 2009). Participants were informed that descriptive data or direct quotations in an anonymous form would be used in dissemination.

4.5.10. Data protection

The research team complied with the Data Protection Act 1998 when sharing or processing data within the NHS and other organisations involved in the research. Study data were accessible via databases on two separate servers. Identifiable data could only be handled by authorised staff members (Chief Investigator, research nurses and support staff with NHS

contracts) via a password protected, secure database on the NHS server. The NHS database handles and stores the identifiable data (patient name, address, postcode, CHI, date of birth, phone numbers, email). This data can only be accessed from an NHS Lothian PC, within the NHS network, by staff members that have been given the appropriate permissions. Anonymised data were also stored on the University server, which could only be only accessed via a password protected secure database. The University server contains the pseudo-anonymised research and audit data, where all the data relates to the LINCHPIN ID, the university system primary numeric identifier.

Paper and other manual files are stored in a locked filing cabinet in a secure area for the purposes of future communication with the participant and their doctor as appropriate. Only the LATCH/LINCHPIN research team, with NHS contracts and a duty of confidentiality, have access to the data.

4.5.11. Possible risk to me as researcher

Many of the interviews took place in the participant's own homes, which meant that I was visiting these participants on my own. A lone working procedure was therefore followed to minimise any risk and to ensure my own safety when visiting participants outside the hospital setting (see Box 10).

Box 10: Lone working procedure

Pre-study visit: Researcher to inform a nominated person (supervisor or other identified member of staff within the LINCHPIN research team) of the planned study visit, and give details of date, location, start time and estimated finish time

During study visit: Nominated person aware of study visit; both researcher and nominated person to be contactable by telephone

Post-study visit: Researcher to contact nominated person once study visit is complete. If no contact is made within the expected time, nominated person will contact researcher

4.6. Patient involvement in research

I involved a group of patient representatives (the Research to Understand Stroke due to Haemorrhage Patient Reference Group (RUSH PRG)) during the design of this study. At the time, the RUSH PRG was comprised of 3 stroke survivors- 2 women and 1 man- two of whom had had an intracerebral haemorrhage. They provided valuable assistance in the development of study materials and reviewed and commented upon the information sheet and consent forms for this study.

4.7. Overview of remaining chapters

This thesis will now be divided into separate methodology and results chapters (Chapters 5-10), each containing study-specific sections based upon the three research objectives. Chapter 11 will then provide a summary of the principal findings, drawing them together with an overall conclusion.

5. Methodology: LATCH COG

The Lothian Audit of the Treatment of Cerebral Haemorrhage (LATCH) is a prospective, population-based cohort study that identified all residents in the Lothian Health board region of Scotland who were diagnosed with first-ever or recurrent ICH (confirmed by brain imaging or pathology), between June 1st 2010 and May 31st 2013 inclusive. In order to study the prevalence of pre-existing dementia and cognitive impairment in patients with ICH, and to quantify their incidence at specific time points thereafter (objective (a)), I carried out a retrospective analysis of LATCH (henceforth referred to as LATCH COG). This chapter contains a detailed discussion of the methods used to collect and analyse data. Strengths and limitations are included at the end of this chapter to aid the reader in interpreting the clinical implications and generalisability of the findings.

5.1. Research objective and questions

The overall aim of LATCH COG was to:

- Study the prevalence of pre-existing dementia and cognitive impairment in patients with ICH, and to quantify their incidence at specific time points thereafter.

To meet this aim, the following research questions were developed:

1. What is the prevalence of pre-existing cognitive impairment and dementia in patients who have had an ICH?
2. What factors are associated with pre-existing cognitive impairment and dementia in patients who have had an ICH?
3. What is the incidence of new-onset cognitive impairment and dementia within 1-5 years of ICH?
4. What factors are associated with new-onset cognitive impairment and dementia in patients who have had an ICH?

5. How accurate is the GP electronic medical record for identifying cognitive impairment and/or dementia, compared to a reference standard of the IQCODE?

5.2. Selection of Participants

Participants were included in LATCH COG if they met the inclusion criteria outlined in Box 11.

Box 11: LATCH COG inclusion criteria

Participants were eligible if they were:

- Diagnosed as having first-ever 'primary' ICH (not secondary to an underlying tumour, intracranial vascular malformation or venous thrombosis etc):

ICH was defined as the abrupt symptomatic onset of severe headache, altered level of consciousness, or focal neurological deficit, anatomically referable to a focal collection of blood within the brain parenchyma as observed on brain imaging (by a neuroradiologist with an interest in stroke) or at autopsy, which was not attributable to prior trauma or haemorrhagic conversion of a cerebral infarction

- Adults, aged 16 or over at time of diagnosis
- Seen as an inpatient or neurovascular outpatient at Western General Hospital, Royal Infirmary Edinburgh or St John's Hospital
- Resident in the NHS Lothian Healthboard region
- Included in the Lothian Audit of the Treatment of Cerebral Haemorrhage
- Diagnosed with ICH between June 2010 and May 2013
- Given a CT scan at time of index ICH

Participants were excluded from LATCH COG if they met any of the exclusion criteria outlined in Box 12.

Box 12: LATCH COG exclusion criteria

Participants were excluded if they had:

- ICH definitely attributable to trauma
- Exclusively extra-axial intracranial haemorrhage (i.e. subarachnoid, subdural, or extradural). However, patients with intraparenchymal haemorrhage that extended into other compartments could be included.
- ICH into a tumour, from a proven intracranial vascular malformation, due to venous sinus thrombosis, or which proves to be a haemorrhagic transformation of a cerebral infarction after further imaging or autopsy.
- Recurrent ICH
- Opted out of LATCH

5.3. Methods

Patients meeting the eligibility criteria above were identified using the LATCH database. LATCH is an audit of the care of adults who were affected by ICH. As part of this audit, the team collected copies of the patient's primary care records, including GP summaries, at baseline and during follow-up. In clinical practice, GP summaries are used in order to give an indication of the patient's significant co-morbidities, home or telephone consultations, repeat prescriptions, a list of medications from the last 3 months, any allergies or intolerances, and any related health history i.e. blood pressure, height, weight, history of smoking etc. Once the patient had died, the team collected copies of the patient's hospital and practitioner services notes.

5.4. Demographic characteristics and medical history

In addition to collecting data on age and sex, the LATCH research team recorded history of previous stroke or TIA, hypertension, diabetes and atrial fibrillation. Classification for each of these was based on whether the participant had been diagnosed prior to their index ICH and if it was recorded in their primary care or hospital notes. Participants were classified as having hypertension if either a history of hypertension had been documented in their medical records or if they were taking antihypertensive medications at the time of their ICH. Pre-existing level of dependency was evaluated using the modified Rankin scale, where patients with a score of >2 were considered dependent (van Swieten et al 1988).

5.5. Follow-up

Multiple sources of follow-up included an annual review of patient's primary care and hospital records, annual questionnaires that were sent to the patient's GP to determine level of dependency (according to the modified Rankin Scale) and whether there had been any recurrent stroke or new diagnosis of dementia, and review of death certificates (if applicable).

5.6. Evaluation of cognitive impairment and dementia

Primary care and hospital records for each patient were reviewed for the presence of dementia or cognitive impairment before and after their index ICH. This involved hand-searching of the entire record including individual consultations, clinic letters and hospitalisation documentation. Diagnosis was often recorded in hospital notes or clinic letters but not the primary care diagnosis list. In some cases, diagnosis was made on the basis of cognitive impairment that was apparent from hand-searching of the medical record including individual primary care consultations, hospital physician consultations and nursing and allied health professional records.

5.6.1. Definitions

The diagnosis of **dementia** was confirmed following the criteria set out in Box 13, recorded in either the hospital or primary care records.

Box 13: Criteria for the diagnosis of dementia

Diagnosis of dementia was confirmed if there was:

1. Evidence that the DSM-IV criteria have been fulfilled (American Psychiatric Association, 1994):

- Documented evidence of previously normal cognitive and social function,
- Decline of cognitive and social function that was irreversible with medical or psychiatric treatment,
- Evidence of memory impairment,
- Dementia that causes significant impairment in social or occupational functioning and represents a significant decline from previous level of functioning,
- Documented evidence of one or more of the following cognitive disturbances: aphasia, apraxia, agnosia or disturbance in executive function.

2. A READ code used in the GP electronic record diagnostic summary that implied dementia (Dementia Partnerships 2012; Table 7)

3. A prescription of medication intended to enhance cognition (i.e. cholinesterase inhibitors) (Table 8)

The diagnosis of **cognitive impairment** was confirmed following the criteria set out in Box 14, recorded in either the hospital or primary care records.

Box 14: Criteria for the diagnosis of cognitive impairment

Diagnosis of cognitive impairment was confirmed if there was:

1. Evidence that the following conditions for Mild Cognitive Impairment have been met (Albert et al, 2011):

- Concerns regarding a change in cognition,

- Impairment in one or more cognitive domains,
- Preservation of independence in functional abilities,
- not demented.

2. A READ code used in the GP electronic record diagnostic summary that indicates a non-specific cognitive problem, for example: memory loss symptom, mental disorder, cognitive impairment, cognitive decline, confusional state, memory disturbance or memory loss of elderly.

If there was no mention of any of the above, the patient was categorised as having no history of dementia. The classifications for dementia on the study database were as follows:

1. Diagnosis of dementia;
2. Cognitive impairment (no dementia); or
3. No history of dementia.

Table 7: Dementia specific READ Codes

READ Code	Description
E012.11, Eu10711	Alcoholic dementia NOS
Eu00z11	Alzheimer's dementia unspecified
Eu00111	Alzheimer's disease type 1
Eu00013	Alzheimer's disease type 2
Eu004, Eu01.11	Arteriosclerotic dementia
E004100	Arteriosclerotic dementia with delirium
E004200	Arteriosclerotic dementia with paranoia
E004300	Arteriosclerotic dementia with depression
E004z00	Arteriosclerotic dementia NOS
Eu00, F110.00	Dementia in Alzheimer's Disease
Eu000, F110000	Dementia in Alzheimer's Disease with early onset
Eu001, F110100	Dementia in Alzheimer's Disease with late onset
Eu00200	Dementia in Alzheimer's Disease, atypical or mixed type
Eu00z	Dementia in Alzheimer's Disease, unspecified
Eu021	Dementia in Creutzfeldt-Jacob Disease
Eu022	Dementia in Huntington's Disease
Eu023	Dementia in Parkinson's Disease
Eu024	Dementia in Human Immunodeficiency Virus (HIV) Disease
E02y1	Drug-induced dementia
Eu025, F116.00	Lewy body dementia

READ Code	Description
Eu013	Mixed cortical and subcortical vascular dementia
Eu011, Eu004.11	Multi-infarct dementia
E012.00	Other alcoholic dementia
Fyu3000	Other Alzheimer's disease
Eu01y	Other vascular dementia
Eu020, F111.00	Pick's disease/ Frontotemporal dementia
Eu00011	Presenile dementia; Alzheimer's Type
Eu00012	Primary degenerative dementia; Alzheimer's type; presenile onset
EU00113	Primary degenerative dementia of Alzheimer's type; senile onset
Eu00112	Senile dementia; Alzheimer's type
Eu012	Subcortical vascular dementia
Eu01.00	Vascular Dementia
Eu010	Vascular dementia of acute onset
Eu01z	Vascular dementia, unspecified

Table 8: List of medications to enhance cognition

Medication	Brand Name
Donepezil	Aricept, Aricept Evess
Galantamine	Reminyl, Reminyl XL
Rivastigmine	Exelon
Memantine hydrochloride	Exiba

Dementia and cognitive impairment were defined as pre- or post-event according to whether the diagnosis was made before or after the index ICH. The term cognitive decline is used in this thesis when referring to a grouping of patients with either cognitive impairment or dementia.

Based on evidence that less than half of people with dementia in the UK are ever formally diagnosed with dementia, GP summaries held in the LATCH audit records were supplemented by IQCODE questionnaires for the sub-set of patients who were also in the LINCHPIN research study (Iliffe et al 2009; Connolly et al 2011). The IQCODE can be very useful in the screening and evaluation of dementia. This questionnaire is rated by a relative, who is asked to compare the participant's ability to perform a list of daily tasks requiring memory and other intellectual abilities with his or her baseline 10 years prior to the index

event. IQCODE scores between 53 and 63 were classified as cognitive impairment with no dementia, and pre-existing dementia was recorded as an IQCODE score of 64 and above (Jorm 1994). The IQCODE allowed for the validation of the medical records-based assessments for the presence of cognitive impairment and/or dementia before ICH.

5.7. Radiological assessment

Brain CT scans were available for all patients on admission. At least one neuroradiologist evaluated CT images with a standardised pro forma derived from previous largescale stroke studies (Rodrigues et al, 2018). Using the CT scans, the following data were recorded:

- location of haemorrhage (lobar or non-lobar)
- haemorrhage volume
- presence or absence of old vascular lesions (lacunes)
- severity of anterior and posterior white matter lucencies (3-point rating scale with a higher score denoting more severe white matter lucencies (van Swieten et al, 1990))
- severity of central (deep) or cortical cerebral atrophy (3-point rating scale where a higher score denotes a more severe atrophy (Sato et al, 2016))
- composite SVD score (one point for each of the following: >1 lacune, severe white matter lucencies and severe atrophy)

5.7.1. Definition of lobar and non-lobar ICH

ICH location was defined as either 'lobar' or 'non-lobar'. At least one experienced consultant neuroradiologist reviewed diagnostic brain imaging and classified ICH location as 'non-lobar' if an adult had a single infratentorial ICH (located in the brainstem or cerebellum), a single supratentorial deep ICH (located in the basal ganglia, internal or external capsule or thalamus without extension to a lobar area), or multiple ICHs in solely non-lobar locations (either supratentorial deep or infratentorial). All other ICHs were 'lobar'.

5.7.2. Hematoma volume

Hematoma volume was calculated using the first CT brain scan after the adult's presentation with ICH using the ABC/2 method where: A is the largest diameter of ICH on in the axial plane (cm); B is the largest diameter at 90 degrees to A on the same slice (cm) and; C is the depth of the haemorrhage as measured by the number of axial CT slices on which the ICH is visible (cm) (Newman 2007).

5.7.3. Composite CT SVD score

A team of researchers from the Third International Stroke Trial created an aggregate small vessel disease score by summing white matter changes, presence of lacunes and brain atrophy scores. White matter changes were rated with the Van Swieten Scale, where the posterior (range 0-2) and anterior (range 0-2) scores were combined into a 5-point ordinal scale (0-4) (van Swieten et al, 1990). The presence and number of lacunes was recorded and brain atrophy was defined as central (deep) or cortical and rated with a 3-point ordinal scale as: none, moderate, or severe (Sato et al, 2016). One point was assigned for each of the following if present: severe lucencies (Van Swieten Scale = 2) in anterior or posterior white matter, lacunes >1, and severe (=2) central or cortical atrophy. The combined 4-point ordinal score therefore assessed the global burden of small vessel disease from 0 (no imaging features of severe SVD) to 3 (imaging features of SVD scored as severe for each imaging variable) (Arba et al, 2017).

5.7.4. Edinburgh CAA criteria

For patients who had a lobar ICH, the Edinburgh CT and genetic diagnostic criteria for CAA was also available (Rodrigues et al, 2018). The Edinburgh CAA criteria can predict the likelihood of underlying moderate/severe CAA. For the Edinburgh CAA criteria (CT only), scores were based on the absence or presence of subarachnoid haemorrhages and finger-like projections (elongated extensions arising from the haematoma, longer than they are wide, regardless of whether they extended to the cortex or not). For the Edinburgh CAA criteria (CT and APOE genotype), scores were based on the absence or presence of subarachnoid haemorrhages, finger-like projections and possession of the Apolipoprotein E

(APOE) $\epsilon 4$ allele². A low score signified that none of the features were present and a high score signified that at least two- or both for the CT only criteria- of the features were present.

5.8. Statistical Analysis

SPSS statistical software was used to conduct statistical analyses. The analysis of data were carried out separately for each of the research questions as outlined below.

1. What is the prevalence of pre-existing cognitive impairment and dementia in patients who have had an ICH?

Using descriptive statistics, the prevalence of cognitive impairment with no dementia and pre-existing dementia is described with 95% confidence intervals (CI).

2. What factors are associated with pre-existing cognitive impairment and dementia in patients who have had an ICH?

According to the scale of variances, differences in clinical as well as imaging features between the three ICH groups ('no cognitive decline, 'pre-existing cognitive impairment (no dementia)' and 'pre-existing dementia') were compared with bivariate analyses (Pearson Chi-square tests or Kruskal-Wallis tests where appropriate). Continuous data are reported as medians and inter-quartile range (IQR). Categorical data are presented as frequencies and percentages.

To determine which of the variables above were potential risk factors, separate binomial logistic regressions were performed for those with pre-existing cognitive decline (cognitive impairment or dementia) and pre-existing dementia only (7-10 events per variable).

² For APOE genotype analysis, the research team obtained DNA from peripheral blood samples or cerebellar tissue stored in the LINCHPIN brain bank. APOE genotype was classified as APOE $\epsilon 4$ possession if they had at least one $\epsilon 4$ allele.

3. What is the incidence of new-onset cognitive decline and dementia within 1-5 years of ICH?

After the exclusion of prestroke cognitive decline, Kaplan-Meier survival analyses (Kaplan and Meier 1958) was used to determine the proportion of patients surviving free of cognitive decline or dementia 1-5 years after their ICH.

4. What factors are associated with new-onset cognitive decline and dementia in patients who have had an ICH?

To investigate differences in survival distributions between baseline characteristics and those at risk of developing new-onset cognitive decline (cognitive impairment or dementia) within 5 years of their stroke, univariate analysis was conducted using the log-rank test (Savage 1956). Using Cox proportional hazards regression models (Cox 1972), separate multivariate analysis was then performed to explore independent factors on the presence of new-onset cognitive decline and new-onset dementia (7-10 outcome events per predictor variable).

5. How accurate is the GP electronic medical record for identifying cognitive decline and/or dementia, compared to a reference standard of the IQCODE?

Using descriptive statistics, patient's pre-ICH cognitive status according to their electronic medical records were compared with the results of the IQCODE.

5.9. Strengths and limitations

Strengths of the study include its prospective, community-based design, with multiple overlapping sources of case ascertainment and comprehensive data collection. The study is based on an unselected cohort of consecutive patients, in a representative population. The LATCH research team examined exclusively a cohort of ICH patients and used standardised data collection.

In stroke cohorts, death occurring during follow-up can be a serious competing risk. Therefore, I decided to take this into account during the survival analysis.

The main strength of this study is the detailed neuroimaging description of structural markers of CAA and SVD in the context of pre- and post-ICH cognitive decline. However, a major limitation is that it did not include MRI data to support the diagnosis of any underlying CAA.

Another limitation is that there were no standardised assessments of cognitive impairment. Pre-existing and new-onset cognitive impairment and dementia were classified based on medical records alone. Although I tried to correct for this by hand searching of the entire GP consultation record including individual consultation records and all hospital clinic and discharge letters to look for evidence of cognitive impairment satisfying the DSM-IV criteria for dementia, given that dementia is consistently underdiagnosed in primary care settings, the prevalence of cognitive impairment and dementia may be higher than that demonstrated for this cohort.

6. Results: LATCH COG

6.1. Study population

The study population consisted of 404 patients (219 females; 54%; 95% CI 49-59%) with a median age of 77 years (interquartile range 68-84), all of which had available CT data from the time of their index ICH. Within the seven-year follow-up period, 312 patients died (77%; 95% CI 73-81%). One hundred and ninety-nine patients had a lobar haemorrhage (49%; 95% CI 44-54%) and 205 patients had a non-lobar haemorrhage (51%; 95% CI 46-56%).

6.2. Prevalence of pre-existing cognitive decline and dementia

Ninety-three patients had pre-existing cognitive decline (23%; 95% CI 19-27%).

Forty-one patients (10%; 95% CI 7-14%) had cognitive impairment with no dementia. The prevalence of cognitive impairment with no dementia was 11% in the lobar group (22 patients; 95% CI 7-16%) and 9% in the non-lobar ICH group (19 patients; 95% CI 6-14%).

Fifty-two patients met the criteria for pre-existing dementia (13%; 95% CI 10-17%). The prevalence of pre-existing dementia was 19% in the lobar group (37 patients; 95% CI 13-25%) and 7% in the non-lobar ICH group (15 patients; 95% CI 4-12%).

6.3. Factors associated with pre-existing cognitive decline and dementia

The following variables include known predictors of dementia for stroke patients and the elderly population in general and were available for analysis (Baumgart et al, 2015; Zulkifly et al, 2016): age, sex, hypertension, diabetes, atrial fibrillation, previous ischaemic stroke or TIA, modified Rankin score, ICH location (lobar vs non-lobar), haemorrhage volume, presence of old vascular lesions, presence of anterior or posterior white matter lucencies, rating of central and cortical atrophy and composite SVD score. For the subgroup of patients where data were available, the Edinburgh CAA criteria (CT only) and Edinburgh CAA criteria (CT and APOE genotype) variables were also selected.

Differences in clinical as well as CT imaging features between the three ICH groups ('no cognitive decline, 'Pre-existing cognitive impairment (no dementia)' and 'pre-existing dementia') were compared with univariate analyses to test for significance.

To determine whether there were statistically significant differences between the three ICH groups and the continuous and ordinal variables, the Kruskal-Wallis test was conducted (data were not normally distributed according to the Shapiro-Wilk Test). To determine whether there was a difference in distributions between the categorical variables and the three ICH groups, a Chi-squared test was conducted. If any cells had an expected count of less than 5, a Fisher's exact test was applied.

Continuous data are reported as medians and interquartile ranges and categorical data presented as frequencies and percentages. Any missing data are made explicit when presenting results. The majority of missing data are related to analysis using the Edinburgh CAA criteria as this only applied to patients who had a lobar ICH. In addition, information relating to genotyping was only available for patients who had consented to the LINCHPIN study.

When conducting multiple analyses on the same dependent variable, the chance of committing a Type I error- rejecting the null hypothesis when you should not- increases, thus increasing the likelihood of observing a significant result by pure chance. To correct for this, or protect from Type I error, a Bonferroni correction was conducted (Bland and Altman 1995). The new p-value will be the alpha-value ($\alpha_{\text{original}} = .05$) divided by the number of comparisons (15): ($\alpha_{\text{altered}} = .05/15 = .003$). To determine if any of the 15 comparisons is statistically significant, the p-value must be $p \leq .003$ (see Tables 9 and 10 for results of univariate analyses).

Table 9: Characteristics of patients with no cognitive decline, with pre-existing cognitive impairment (no dementia) and with pre-existing dementia

	No cognitive decline (n= 311) (%)	Pre-existing cognitive impairment (no dementia) (n= 41) (%)	Pre-existing dementia (n= 52) (%)	p
<i>Demographics</i>				
Age ^a	75 (65-83)	80 (74-85)	82 (78-87)	<.0001
Female sex	163 (52)	22 (54)	34 (65)	.220
<i>Vascular Risk Factors</i>				
Hypertension	207 (67)	28 (68)	31 (60)	.584
Diabetes ^b	34 (11)	7 (17)	5 (10)	.478
<i>Medical History</i>				
Atrial Fibrillation	68 (22)	6 (15)	15 (29)	.257
Previous ischaemic stroke or TIA	67 (22)	15 (37)	14 (27)	.088
<i>Functional Status</i>				
modified Rankin ^a	1 (0-2)	2 (1-3)	3 (2-3)	<.0001
<i>Radiological data</i>				
ICH Location				.002
Non-lobar	171 (55)	19 (46)	15 (29)	
Lobar	140 (45)	22 (54)	37 (71)	
Volume (ml) ^a	18 (5-48)	16 (4-61)	40 (14-90)	.003
Old vascular lesion	127 (41)	22 (54)	24 (46)	.259
Anterior wm lucencies score ^a	1 (1)	1 (1-2)	2 (1-2)	<.001
Posterior wm lucencies score ^a	1 (0-2)	2 (1-2)	2 (1-2)	<.001
Central atrophy score ^a	1 (0-1)	1 (1-2)	1 (1)	<.001
Cortical atrophy score ^a	1 (0-1)	1 (1-2)	1 (1-2)	.080
Composite SVD score ^a	1 (0-2)	1 (1-2)	1 (1-2)	.001

^aMedian (interquartile range, Kruskal-Wallis test); ^bFisher's Exact test

Table 10: Edinburgh CAA criteria data for lobar ICH patients with no cognitive decline, with cognitive impairment (no dementia) and with pre-existing dementia

	No cognitive decline (n= 140) (%)	Pre-existing cognitive impairment (no dementia) (n= 22) (%)	Pre-existing dementia (n= 37) (%)	<i>p</i>
Edinburgh CAA criteria (CT only) ^a				.005
Low	44 (31)	7 (32)	3 (8)	
Intermediate	73 (52)	10 (45)	19 (51)	
High	23 (16)	5 (23)	15 (41)	
Edinburgh CAA criteria (CT & APOE) ^{ab}				.797
Low	11 (8)	2 (9)	1 (3)	
Intermediate	23 (16)	5 (23)	4 (11)	
High	19 (14)	3 (14)	6 (16)	

^a Fisher's Exact test; ^b Missing data for 125 patients

After testing that the distribution of scores was similar for all groups (as assessed by visual inspection of boxplots), both median age ($\chi^2(2) = 29.967$; $p = <.001$) and haemorrhage volume ($\chi^2(2) = 11.445$; $p = 0.003$) were statistically significant between the three ICH groups. Where a statistically significant difference was found, pairwise comparisons were then performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons with those variables. Adjusted p-values and median values are presented below.

Post hoc analysis revealed statistically significant differences in median age between:

- 'no cognitive decline' (75.0) and 'pre-existing cognitive impairment (no dementia)' (80.0) ($p = 0.049$)
- 'no cognitive decline' (75.0) and 'pre-existing dementia' (82.0) ($p = <.0001$)

Post hoc analysis revealed statistically significant differences in median haemorrhage volume between:

- 'pre-existing cognitive impairment (no dementia)' (15.6) and 'pre-existing dementia' (40.2) ($p = 0.033$)
- 'no cognitive decline' (17.7) and 'pre-existing dementia' (40.2) ($p = 0.003$)

For those variables where the distribution of scores was not similar for all groups (as assessed by visual inspection of boxplots), a comparison of distributions was made. The distribution of anterior ($\chi^2(2) = 33.379$; $p = <0.001$) and posterior ($\chi^2(2) = 17.176$; $p = <0.001$) white matter lucencies scores, central atrophy scores ($\chi^2(2) = 19.847$; $p = <0.001$), SVD scores ($\chi^2(2) = 14.461$; $p = 0.001$) and modified Rankin scores ($\chi^2(2) = 79.995$; $p = <0.001$) were statistically significant between the three ICH groups. Where a statistically significant difference was found, pairwise comparisons were then performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons with those variables. Adjusted p-values are presented below.

Post hoc analysis revealed statistically significant differences in anterior white matter lucencies scores between:

- 'no cognitive decline' and 'pre-existing cognitive impairment (no dementia)' ($p = 0.002$),
- 'no cognitive decline' and 'pre-existing dementia' ($p = <.0001$)

Post hoc analysis revealed statistically significant differences in posterior white matter lucencies scores between:

- 'no cognitive decline' and 'pre-existing cognitive impairment (no dementia)' ($p = 0.019$)
- 'no cognitive decline' and 'pre-existing dementia' ($p = 0.002$)

Post hoc analysis revealed statistically significant differences in central atrophy scores between:

- 'no cognitive decline' and 'pre-existing cognitive impairment (no dementia)' ($p = 0.006$)
- 'no cognitive decline' and 'pre-existing dementia' ($p = 0.001$)

Post hoc analysis revealed statistically significant differences in small vessel disease scores between:

- 'no cognitive decline' and 'pre-existing cognitive impairment (no dementia)' ($p = 0.030$)
- 'no cognitive decline' and 'pre-existing dementia' ($p = 0.006$)

Post hoc analysis revealed statistically significant differences in modified Rankin scores between:

- 'no cognitive decline' and 'pre-existing cognitive impairment (no dementia)' ($p = 0.001$)
- 'no cognitive decline' and 'diagnosis of dementia' ($p = <.001$)
- 'pre-existing cognitive impairment (no dementia)' and 'pre-existing dementia' groups ($p = 0.003$)

For those categorical variables where a statistically significant difference was shown, Cramer's V test was then run to provide an estimate of the effect size. See Box 15 for suggested guidelines on how to interpret Cramer's V (Cohen 1998).

Box 15: Cramer's V magnitude of effect size

Magnitude of effect size	Value of Cramer's V
Small	0.1
Moderate	0.3
Large	0.5

Statistically significant differences were found between the following variables and the three ICH groups: ICH location ($\chi^2(4) = 12.531$; $p = 0.002$) and Edinburgh CAA criteria (CT only) ($\chi^2(4) = 14.397$; $p = 0.005$). The effect size was small for both variables, where Cramer's V = 0.176 for ICH location and 0.188 for Edinburgh CAA criteria (CT only).

To determine which of the variables above were potential risk factors, separate binomial logistic regressions were performed for those with pre-existing cognitive decline (cognitive impairment or dementia) and pre-existing dementia only (7-10 events per variable). The following variables, chosen from the results of the literature review (Section 2.2, Table 4), were included in the logistic regression model for cognitive decline: age, sex, location of the haemorrhage (lobar vs non-lobar), haemorrhage volume, presence of old vascular lesions, presence of anterior and posterior white matter lucencies, rating of central and cortical atrophy and composite SVD score.

To ensure that the assumptions of the logistic regression were met, a test for multicollinearity was first performed. The Variance Inflation Factor (VIF) values were well below 10 (suggesting that the variance of the regression coefficient had not been inflated due to multicollinearity in the model) and the tolerance statistics all above 0.2 (indicating a low threat of multicollinearity) (Myers 1990; Menard 1995). Linearity of the continuous variables with respect to the logit of the dependent variable was also assessed via the Box-Tidwell procedure (Box and Tidwell 1962). Based on this assessment, both continuous independent variables (age and haematoma volume) were found to be linearly related to the logit of the dependent variable. To assess for outliers, patients with studentized residual values greater than 2.5 were inspected to determine whether they needed to be removed from the analysis. There were five studentized residuals with values between 2.715 and 9.388 standard deviations which were kept in the analysis after inspecting that the Cook's distance and leverage values were within a normal range.

The logistic regression model was statistically significant, $\chi^2(10) = 71.474$, $p = <0.001$. The model explained 25% (Nagelkerke R^2) of the variance in pre-existing cognitive decline and correctly classified 76% of cases. Sensitivity was 16% and specificity was 94%. According to the Hosmer-Lemeshow test, the model is also a good fit ($p = 0.748$) as it is not statistically significant.

The area under the ROC curve (Figure 5) was .779 (95% CI .731-.828), which is an acceptable level of discrimination according to Hosmer, Lemeshow and Sturdivant (2013). Here, discrimination is the ability of the logistic regression model to distinguish between those patients with and without the event of interest (i.e. be able to predict who had, or did not have, pre-existing cognitive decline).

Of the ten predictor variables, only four were statistically significant: age, lobar ICH location, haemorrhage volume and presence of central atrophy (Table 11).

Figure 5: ROC curve for pre-existing cognitive decline

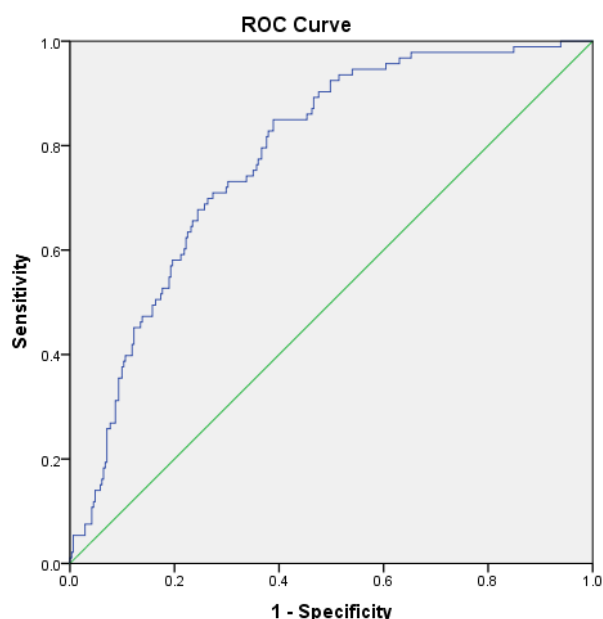


Table 11: Results of binomial logistic regression model for pre-existing cognitive decline

Variable	<i>p</i>	Adjusted Odds Ratio	95% CI for Odds Ratio	
			Lower	Upper
Age, per 1-year increase	.004	1.05	1.02	1.08
Female sex	.901	1.04	.60	1.78
Lobar haemorrhage	.003	2.32	1.34	4.02
Haematoma volume, per 1ml increase	.017	1.01	1.00	1.01
Old vascular lesion	.523	1.20	.69	2.06
Anterior white matter lucencies	.546	1.34	.49	3.90
Posterior white matter lucencies	.313	1.53	.67	3.46
Central atrophy	.001	4.50	1.81	11.16
Cortical atrophy	.981	.99	.51	1.92
SVD score >0	.122	1.80	.86	3.78

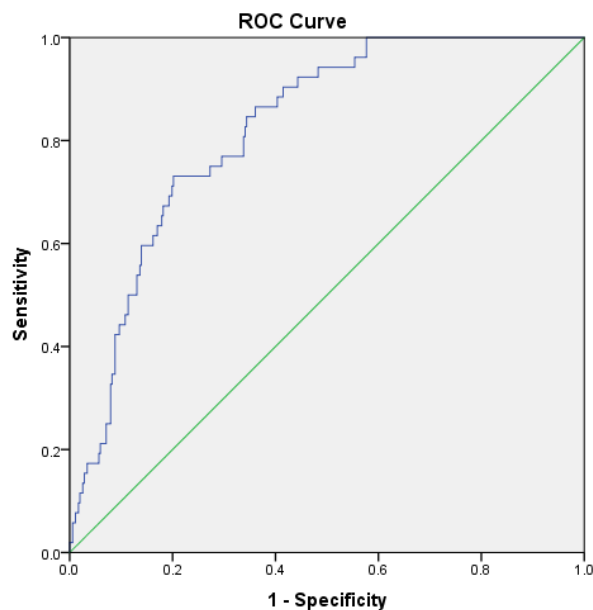
Patients who had a lobar ICH were twice as likely to exhibit pre-existing cognitive decline than those who had a non-lobar ICH, and patients with central atrophy were over 4 times more likely to exhibit cognitive decline than those without. Increasing age was also associated with an increased likelihood of patients having cognitive decline prior to their stroke, as was a larger haemorrhage volume.

The following variables, chosen from the results of the literature review (Section 2.2, Table 4) were included in the logistic regression model for dementia only: age, sex, location of the haemorrhage (lobar vs non-lobar), haemorrhage volume, presence of central atrophy and composite small vessel disease score.

To ensure that the assumptions of the logistic regression were met, a test for multicollinearity was first performed. The VIF values were well below 10 (Menard 1995) and the tolerance statistics all above 0.2 (Myers 1990). Linearity of the continuous variables with respect to the logit of the dependent variable was also assessed via the Box-Tidwell procedure (Box and Tidwell 1962). Based on this assessment, both continuous independent variables (age and haematoma volume) were found to be linearly related to the logit of the dependent variable. To assess for outliers, patients with studentized residual values greater than 2.5 were inspected to determine whether they needed to be removed from the analysis. There were thirteen studentized residuals with values between 2.637 and 4.345 standard deviations, which were kept in the analysis after inspecting that the Cook's distance and leverage values were within a normal range.

The logistic regression model was statistically significant, $\chi^2(6) = 63.967$, $p = <0.001$. The model explained 27% (Nagelkerke R^2) of the variance in pre-existing dementia and correctly classified 87% of cases. Sensitivity was 8% and specificity was 99%. According to the Hosmer-Lemeshow test, the model is also a good fit ($p = 0.472$). The area under the ROC curve (Figure 6) was .821 (95% CI .771-.872), which is excellent level of discrimination according to Hosmer, Lemeshow and Sturdivant (2013).

Figure 6: ROC curve for pre-existing dementia



Of the six predictor variables, five were statistically significant: lobar ICH location, presence of central atrophy, composite SVD score >0, haemorrhage volume and age (Table 12).

Table 12: Results of binomial logistic regression model for pre-existing dementia

Variable	<i>P</i>	Adjusted Odds Ratio	95% CI for Odds Ratio	
			Lower	Upper
Female sex	.528	1.24	.634	2.43
Age, per 1-year increase	.001	1.07	1.03	1.12
Lobar haemorrhage	.002	3.06	1.51	6.22
Haematoma volume, per 1ml increase	.004	1.01	1.00	1.02
SVD score > 0	.028	2.71	1.11	6.60
Central atrophy	.002	8.23	2.15	31.57

Patients who had a lobar ICH were 3 times more likely to exhibit pre-existing dementia than those who had a non-lobar ICH, while patients with evidence of central atrophy were 8 times more likely to exhibit dementia before their stroke than those without. Increasing age and haemorrhage volume were also associated with an increased likelihood of patients having dementia prior to their stroke, as were patients with evidence of small vessel disease.

6.4. Incidence of new-onset cognitive decline and dementia within 1-5 years of first-ever ICH

After excluding patients with prestroke cognitive impairment and dementia from the cohort above, Kaplan-Meier survival analyses methods were used to determine the proportion of patients surviving free of cognitive decline (cognitive impairment or dementia) after their ICH (Kaplan and Meier 1958). A separate analysis was then conducted to determine the proportion of patients surviving free of dementia. For every year of follow-up, the Kaplan-Meier method estimates the probability of patients surviving free of cognitive decline past that given time-point, taking into consideration the presence of censored cases (i.e. patients who die or are lost to follow-up).

Of the 404 patients, 93 were excluded from this part of the analysis due to pre-existing cognitive decline. The study population for the survival analysis is therefore 311 patients (163 [52%] are female), with a median age of 75 years (IQR 65-83). 140 patients had a lobar haemorrhage (45%; 95% CI 40-51%), 171 patients had a non-lobar haemorrhage (55%; 95% CI 49-61%) (see Table 13 and 14 for baseline characteristics of patients without pre-existing cognitive decline).

Table 13: Baseline characteristics of study population, excluding those with prestroke cognitive decline

	No evidence of cognitive decline (n= 249) (%)	New-onset cognitive impairment or dementia (n= 62) (%)	New-onset dementia (n=26) (%)
<i>Demographics</i>			
Age	76 (65-83)	75 (66-81)	79 (74-84)
Female sex	131 (53)	32 (52)	17 (65)
<i>Vascular Risk Factors</i>			
Hypertension	167 (67)	40 (65)	17 (65)
Diabetes	27 (11)	7 (11)	3 (12)
<i>Medical History</i>			
Atrial Fibrillation	54 (22)	14 (23)	6 (23)
Previous ischaemic stroke or TIA	54 (22)	13 (21)	8 (31)

		No evidence of cognitive decline (n= 249) (%)	New-onset cognitive impairment or dementia (n= 62) (%)	New-onset dementia (n=26) (%)
<i>Functional Status</i>				
	modified Rankin >2	39 (16)	9 (15)	6 (23)
<i>Radiological data</i>				
	ICH Location			
	Non-lobar	144 (58)	27 (44)	10 (39)
	Lobar	105 (42)	35 (57)	16 (62)
	Volume (ml)	21 (6-55)	11 (3-24)	8 (2-31)
	Old vascular lesion	101 (41)	26 (42)	13 (50)
Anterior wm lucencies	0	62 (25)	11 (18)	2 (8)
	1	125 (50)	41 (66)	19 (73)
	2	62 (25)	10 (16)	5 (19)
Posterior wm lucencies	0	91 (37)	21 (34)	4 (15)
	1	54 (22)	16 (26)	9 (35)
	2	104 (42)	25 (40)	13 (50)
Central atrophy score	0	75 (30)	19 (31)	7 (27)
	1	141 (57)	37 (60)	16 (62)
	2	33 (13)	6 (10)	3 (12)
Cortical atrophy score	0	70 (28)	17 (27)	4 (15)
	1	127 (51)	37 (60)	17 (65)
	2	52 (21)	8 (13)	5 (19)
Composite SVD score	0	95 (38)	27 (44)	9 (35)
	1	90 (36)	21 (34)	9 (35)
	2	53 (21)	11 (18)	6 (23)
	3	11 (4)	3 (5)	2 (8)

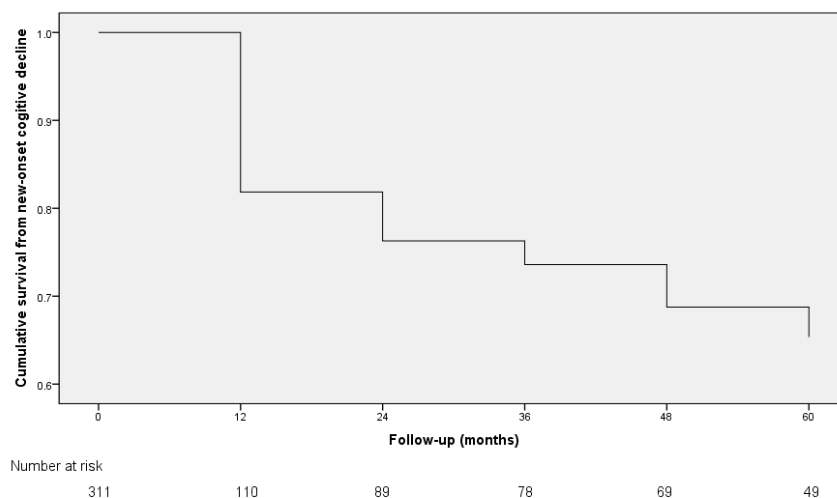
Table 14: Edinburgh CAA criteria data for lobar ICH patients, excluding those with prestroke cognitive decline

	No evidence of cognitive decline (n= 105) (%)	New-onset cognitive impairment or dementia (n= 35) (%)	New-onset dementia (n=16) (%)
Edinburgh CAA criteria (CT only)			
Low	32 (30)	12 (34)	6 (38)
Intermediate	54 (51)	19 (54)	8 (50)
High	19 (18)	4 (11)	2 (13)
Edinburgh CAA criteria (CT & APOE) ^a			
Low	9 (9)	2 (6)	1 (6)
Intermediate	14 (13)	9 (26)	4 (25)
High	13 (12)	6 (17)	1 (6)

^aMissing data for 97 patients

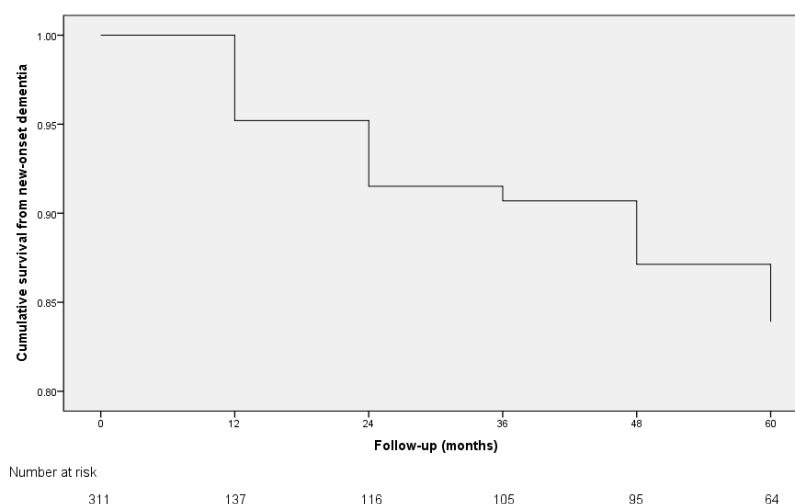
During the first 5 years of follow-up, 60 patients developed new-onset cognitive decline and 222 died (including 30 patients who died after the diagnosis of new-onset cognitive decline). Cumulative survival rates for patients remaining free of cognitive decline were 82% in the first year, and reached 76% at 2 years, 74% at 3 years, 69% at 4 years and 65% at 5 years (see Figure 7).

Figure 7: Survival curve from new-onset cognitive decline



During the first 5 years of follow-up, 24 patients developed new-onset dementia. Cumulative survival rates for patients remaining free of dementia were 95% in the first year, and reached 92% at 2 years, 91% at 3 years, 87% at 4 years and 84% at 5 years (see Figure 8).

Figure 8: Survival curve for new-onset dementia



6.5. Factors associated with new-onset cognitive decline and dementia

To investigate differences in survival distributions between baseline characteristics and those at risk of developing new-onset cognitive decline within 5 years of their stroke, univariate analysis was conducted using the log-rank test (Savage 1956). The log-rank tests the hypothesis that there is no difference in survival times between the groups being studied at any of the time points. The log rank test compares the observed and expected number of events for each group using the same test statistic as the Chi-squared test, although the calculations for the expected frequencies are different. Log-rank tests can only be run with categorical variables as such, any continuous variables had to be categorised. Age and haematoma volume were both dichotomised around the median.

One of the assumptions of the Kaplan-Meier method is that censorship (those who do not experience the event) is similar in all groups tested. It is assumed that censoring is not related to time and that the pattern of censoring is the same in all groups. Failure to meet this assumption can lead to false conclusions being drawn. To detect censoring in each of the variables, I examined the percentage of censored cases per group to determine whether there was a similar amount of censorship.

I could not detect statistically significant results when investigating the differences in survival distributions between baseline characteristics and patients with new-onset cognitive decline (Table 15).

Table 15: Associations of new-onset cognitive decline with baseline characteristics

	n	No. of events	χ^2	p
<i>Demographics and medical history</i>				
Age, >75	75 (65-83)	26	.294	.588
Female sex	163 (52%)	30	.511	.475
Hypertension	207 (67%)	39	.120	.729
Diabetes	34 (11%)	7	1.455	.228
Atrial Fibrillation	68 (22%)	14	.674	.412
Previous ischaemic stroke or TIA	67 (22%)	12	.020	.888
<i>Functional status</i>				
modified Rankin >2 ^a	48 (16%)	9	1.871	.171
<i>Radiological data</i>				
ICH Location			2.888	.089
Non-lobar	171 (55%)	26		
Lobar	140 (45%)	34		
Volume, >18ml	17.7 (5-48.2)	19	.055	.814
Old vascular lesion	127 (41%)	26	1.050	.306
Anterior wm lucencies score >0	238 (77%)	50	3.935	.047
Posterior wm lucencies score >0	199 (64%)	40	3.562	.059
Central atrophy score >0	217 (70%)	43	1.009	.315
Cortical atrophy score >0	224 (72%)	43	.104	.747
Composite SVD score >0	189 (61%)	33	.559	.455
Edinburgh CAA criteria (CT only) ^b	95 (31%)	21	.042	.837
Intermediate/High				
Edinburgh CAA criteria (CT & APOE) ^c	42 (14%)	14	1.622	.203
Intermediate/High				

Data are n (%) or median (IQR). ^a Missing data for 3 patients; ^b Missing data for 171 patients (lobar ICH only); ^c Missing data for 258 patients (lobar ICH only)

However, log-rank tests determined that there were statistically significant differences between those with new-onset dementia and patients who were older in age ($\chi^2(1) = 9.543$; $p = .002$) and had posterior white matter lucencies ($\chi^2(1) = 11.942$; $p = 0.001$) (Table 16; Figures 9 and 10).

Table 16: Associations of new-onset dementia with baseline characteristics

	n	No. of events	χ^2	p
<i>Demographics and medical history</i>				
Age, >75	75 (65-83)	15	9.543	.002
Female sex	163 (52%)	15	.967	.325
Hypertension	207 (67%)	16	.146	.702
Diabetes	34 (11%)	3	1.030	.310
Atrial Fibrillation	68 (22%)	6	.793	.373
Previous ischaemic stroke or TIA	67 (22%)	7	1.904	.168
<i>Functional Status</i>				
modified Rankin >2 ^a	48 (16%)	6	8.215	.004
<i>Radiological data</i>				
ICH Location			2.965	.085
Non-lobar	171 (55%)	9		
Lobar	140 (45%)	15		
Volume, >18ml	17.7 (5-48.2)	8	.213	.645
Old vascular lesion	127 (41%)	12	1.025	.311
Anterior wm lucencies score >0	238 (77%)	23	7.065	.008
Posterior wm lucencies score >0	199 (64%)	21	11.942	.001
Central atrophy score >0	217 (70%)	19	3.030	.082
Cortical atrophy score >0	224 (72%)	20	2.695	.101
Composite SVD score >0	189 (61%)	15	2.520	.112
<i>Edinburgh CAA criteria (CT only)^b</i>				
Intermediate/High	95 (31%)	9	.004	.948
<i>Edinburgh CAA criteria (CT & APOE)^c</i>				
Intermediate/High	42 (14%)	4	.078	.779

Data are n (%) or median (IQR). ^a Missing data for 3 patients; ^b Missing data for 171 patients (lobar ICH only); ^c Missing data for 258 patients (lobar ICH only)

Figure 9: Cumulative survival rates for new-onset dementia according to age

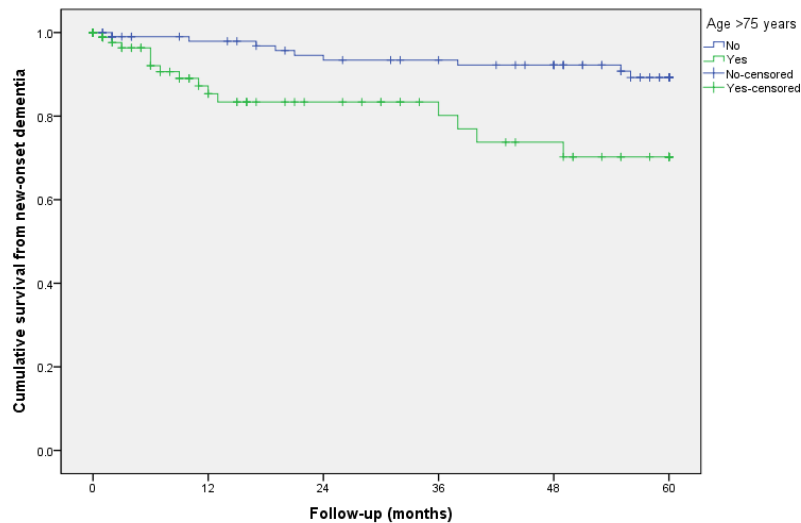
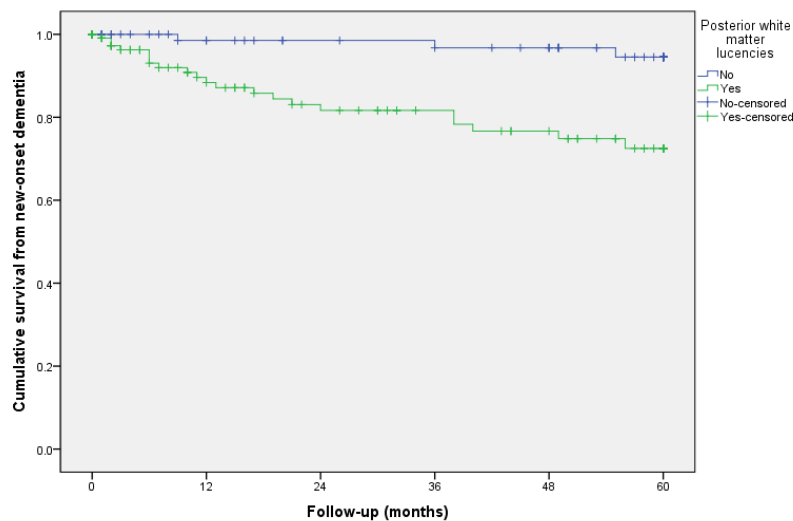


Figure 10: Cumulative survival rates for new-onset dementia in patients with and without posterior white matter lucencies



Using Cox proportional hazards regression model, separate multivariate analysis was then performed to explore independent factors on the presence of new-onset cognitive decline and new-onset dementia only (7-10 outcome events per predictor variable). The Cox's regression procedure is similar to logistic regression and enables the difference between survival times of particular groups of patients to be tested, while allowing for other factors. The main output of the Cox regression model is the hazard ratio (HR), which is given for each independent predictor variable. For example, when comparing those who have had a lobar ICH to those who have had a non-lobar ICH, the hazard is the probability of the event (e.g. new-onset cognitive decline) occurring within a defined time interval, and the hazard ratio is

the ratio between the hazard of the event in the lobar group and the hazard of the event in the non-lobar group.

A key assumption of the Cox regression method is that of proportional hazards. This means that the survival curves for the groups must have hazard functions that are proportional over time. In order to test this assumption, survival curves were plotted for each of the variables to be tested in multivariate analysis and a visual inspection made to ensure that the survival curves did not cross.

The following variables, chosen from the results literature review (Section 2.2, Table 4), were included in the regression model for new-onset cognitive decline: age, sex, location of the haemorrhage, haemorrhage volume, presence of white matter lucencies (anterior and posterior) and composite SVD score >0. The Cox's regression model for new-onset cognitive decline was not statistically significant, $p = 0.111$.

The following variables included in the logistic regression model for new-onset dementia only were age, sex and location of haemorrhage. The Cox's regression model for new-onset dementia was statistically significant, $p = <0.001$. The only independent risk factor for new-onset dementia was increasing age (HR per 1-year increase 1.085; 95% CI 1.039-1.133) (Table 17).

Table 17: Results of Cox regression model of new-onset dementia

Variable	<i>p</i>	Hazard Ratio	95% CI for Hazard Ratio	
			Lower	Upper
Age, per 1-year increase	.000	1.085	1.039	1.133
Female sex	.277	.599	.237	1.509
Lobar haemorrhage	.149	1.851	.802	4.275

6.6. The problem of competing risks

A competing risk is an event that modifies the chance of the event of interest occurring. In the LATCH cohort, death is a major competing risk as it can prevent the observation of new-onset cognitive decline (e.g. a patient may have started to develop cognitive decline, but they died before it was diagnosed by their GP). In this study, death might not only prevent the outcome of interest from occurring, it may also strongly alter its probability.

The primary aim of this PhD is to investigate the long-term outcomes of ICH. We know that over 40% of patients die within the first month of their ICH, after which the risk of death significantly decreases (Fogelholm et al, 2005). As such, log-rank tests and Cox regression models were re-run after excluding those patients who died within the first 30 days after their index ICH.

Of the original cohort of 404 patients, 93 were excluded from this part of the analysis due to pre-existing cognitive decline, and a further 143 were excluded due to death within the first 30 days. The study population for the survival analysis is therefore 168 patients (94 [56%] are female), with a median age of 74 years (IQR 61-82). 82 patients had a lobar haemorrhage (49%; 95% CI 41-57%) and 86 patients had a non-lobar haemorrhage (51%; 95% CI 43-59%).

During the first 5 years of follow-up, 47 patients who survived longer than 30-days after their stroke developed new-onset cognitive decline and 22 developed new-onset dementia. I could not detect statistically significant results when investigating the differences in survival distributions between baseline characteristics and patients with new-onset cognitive decline (Bonferroni corrected significance level of $p \leq .003$) (Table 18).

Table 18: Associations of new-onset cognitive with baseline characteristics in patients who survive past 30 days

	<i>n</i>	No. of events	χ^2	<i>p</i>
<i>Demographics</i>				
Age, >74	83 (49%)	26	4.808	.028
Female sex	94 (56%)	27	.130	.718
<i>Vascular Risk Factors</i>				
Hypertension	107 (64%)	30	.055	.815
Diabetes	15 (9%)	7	4.803	.028
<i>Medical History</i>				
Atrial Fibrillation	36 (21%)	12	1.541	.214
Previous ischaemic stroke or TIA	32 (19%)	10	.193	.661
<i>Functional Status</i>				
modified Rankin >2	21 (13%)	8	4.218	.040
<i>Radiological data</i>				
ICH Location			6.422	.011
Non-lobar	86 (51%)	17		
Lobar	82 (49%)	30		
Volume, >10ml	79 (47%)	24	.579	.447
Old vascular lesion	72 (43%)	20	.031	.860
Anterior wm lucencies score >0	127 (76%)	40	4.711	.030
Posterior wm lucencies score >0	99 (59%)	32	4.440	.035
Central atrophy score >0	116 (69%)	36	3.075	.080
Cortical atrophy score >0	121 (72%)	35	.648	.421
Composite SVD score >0	91 (54%)	27	1.676	.195
Edinburgh CAA criteria (CT only) ^a				
Intermediate/High	52 (64%)	19	.194	.660
Edinburgh CAA criteria (CT & APOE) ^b				
Intermediate/High	32 (56%)	13	2.901	.089

Data are n (%) or median (IQR). ^a Missing data for 87 patients (lobar ICH only); ^b Missing data for 127 patients (lobar ICH only)

However, log-rank tests also determined that there were statistically significant differences between those with new-onset dementia and patients who were older in age ($\chi^2(1) = 12.158$;

$p = <.001$), had a modified Rankin score >2 ($\chi^2(1) = 9.383$; $p = 0.002$) and the presence of posterior ($\chi^2(1) = 10.328$; $p = 0.001$) white matter lucencies (Table 19 and Figures 11-13).

Table 19: Associations of new-onset dementia with baseline characteristics in patients who survive past 30 days

	N	No. of events	χ^2	p
<i>Demographics</i>				
Age, >74	83 (49%)	16	12.158	<.001
Female sex	94 (56%)	15	1.710	.191
<i>Medical History</i>				
Hypertension	107 (64%)	15	.417	.519
Diabetes	15 (9%)	3	1.107	.293
Atrial Fibrillation	36 (21%)	6	1.190	.275
Previous ischaemic stroke or TIA	32 (19%)	6	1.094	.296
<i>Functional Status</i>				
modified Rankin >2	21 (13%)	6	9.383	.002
<i>Radiological data</i>				
ICH Location			1.389	.239
Non-lobar	86 (51%)	9		
Lobar	82 (49%)	13		
Volume, $>10\text{ml}$	79 (47%)	11	.100	.752
Old vascular lesion	72 (43%)	11	.874	.350
Anterior wm lucencies score >0	127 (76%)	21	6.358	.012
Posterior wm lucencies score >0	99 (59%)	19	10.328	.001
Central atrophy score >0	116 (69%)	17	1.838	.175
Cortical atrophy score >0	121 (72%)	19	3.349	.067
Composite SVD score >0	91 (54%)	14	2.588	.108
<i>Edinburgh CAA criteria (CT only)^a</i>				
Intermediate/High	52 (64%)	18	.006	.937
<i>Edinburgh CAA criteria (CT & APOE)^b</i>				
Intermediate/High	32 (56%)	4	.042	.838

Data are n (%) or median (IQR). ^a Missing data for 87 patients (lobar ICH only); ^b Missing data for 127 patients (lobar ICH only)

Figure 11: Cumulative survival rates for new-onset dementia in patients who survive past 30 days according to age

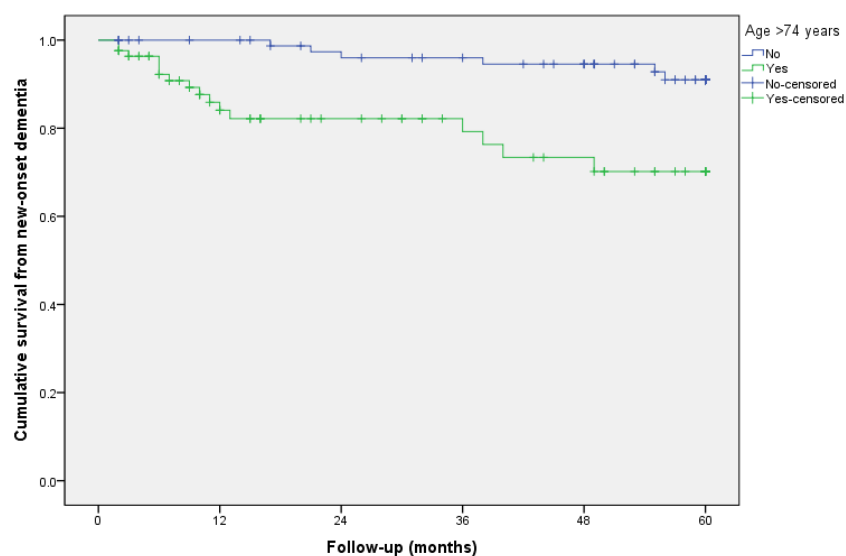


Figure 12: Cumulative survival rates for new-onset dementia in patients who survive past 30 days according to modified Rankin score

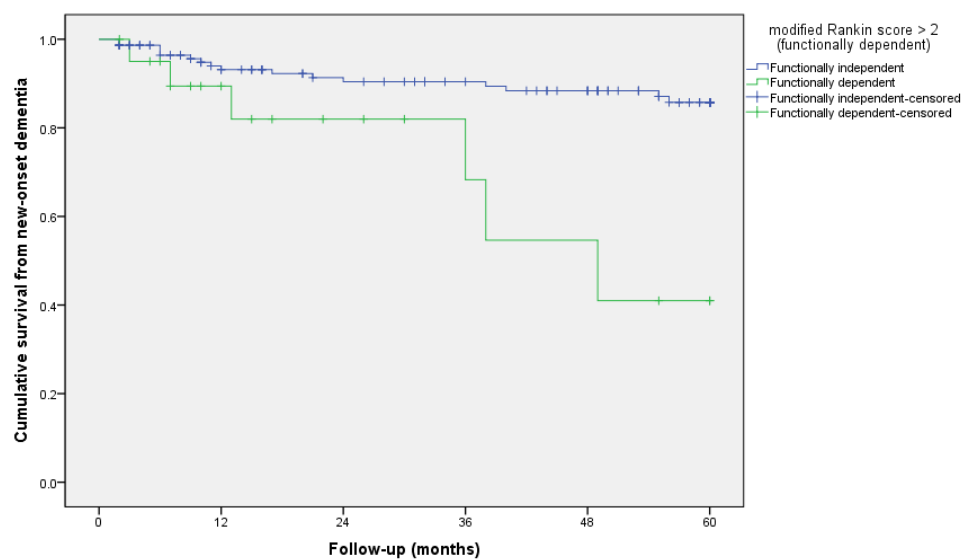
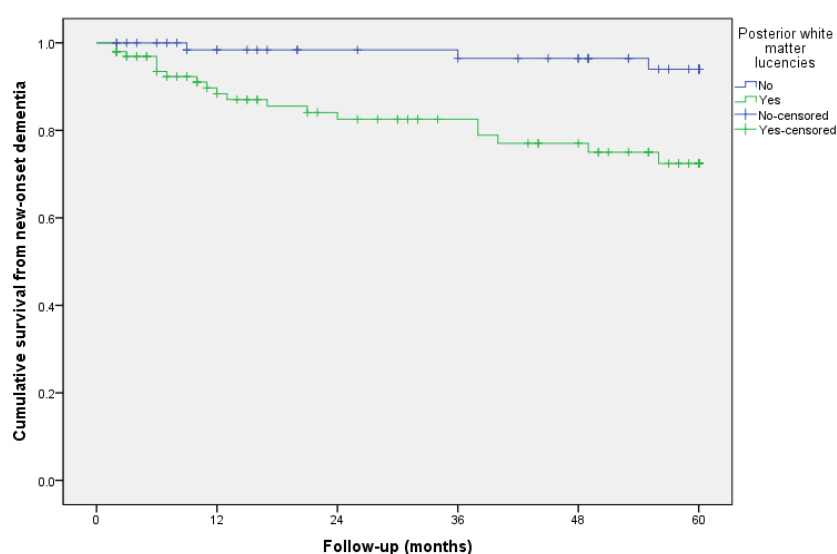


Figure 13: Cumulative survival rates for new-onset dementia in patients who survive past 30 days with and without posterior white matter lucencies



The following variables, chosen from the results of the literature review (Section 2.2, Table 4), were included in the regression model for new-onset cognitive decline: age, sex, location of the haemorrhage, presence of white matter lucencies (anterior and posterior) and composite SVD score >0. The Cox's regression model for new-onset cognitive decline was statistically significant, $p = .010$ (Table 20).

Table 20: Results of Cox regression model of new-onset cognitive decline in patients who survive past 30-days

Variable	p	Hazard Ratio	95% CI for Hazard Ratio	
			Lower	Upper
Age, per 1-year increase	.092	1.025	.996	1.054
Female sex	.321	.720	.376	1.379
Lobar haemorrhage	.011	2.184	1.193	4.000
Anterior white matter lucencies	.167	1.958	.755	5.078
Posterior white matter lucencies	.600	1.241	.554	2.781
Small vessel disease score >0	.993	.997	.500	1.989

The only independent risk factors for new onset cognitive decline was lobar ICH location (HR 2.184; 95% CI 1.193-4.000).

The following variables included in the logistic regression model for new-onset dementia only were age, sex and location of haemorrhage. The Cox's regression model for new-onset dementia was statistically significant, $p = .001$. The only independent risk factor for new-onset dementia was increasing age (HR per 1-year increase 1.083; 95% CI 1.034-1.134) (Table 21).

Table 21: Results of Cox regression model of new-onset dementia in patients who survive past 30-days

Variable	p	Hazard Ratio	95% CI for Hazard Ratio	
			Lower	Upper
Age, per 1-year increase	.001	1.083	1.034	1.134
Female sex	.520	.718	.262	1.969
Lobar haemorrhage	.361	1.490	.633	3.508

6.7. Accuracy of GP electronic medical record for identifying cognitive decline and/or dementia

Using descriptive statistics with those LATCH patients who also consented to the LINCHPIN study, I compared patient's pre-ICH cognitive status according to their medical records with the results of the IQCODE (IQCODE scores between 53 and 63 will be indicative of cognitive impairment with no dementia, and pre-existing dementia will recorded as a score of 64 and above) (Table 22).

In total, 132 patients had an IQCODE recorded. Of those patients with an IQCODE score indicating no history of cognitive decline (74 patients; 56%; 95% CI 47-65%), only 2 were recorded as having a history of cognitive decline in baseline characteristics, and none were recorded as having dementia.

Of those patients with an IQCODE score indicative of pre-existing cognitive decline (37 patients; 28%; 95% CI 21-37%), 27 were recorded as having no history of cognitive decline in baseline characteristics, 6 as having cognitive decline and 4 as having dementia.

Lastly, of those patients with an IQCODE suggestive of pre-existing dementia (21 patients; 16%; 95% CI 10-23%), 4 were recorded as having no history of cognitive decline, 6 as having a cognitive impairment and 11 as having dementia.

Table 22: IQCODE vs medical records

Medical Record	IQCODE score		
	<53	53-63 (suggestive of cognitive impairment)	>63 (suggestive of dementia)
No History of cognitive decline	72	27	4
History of cognitive impairment	2	6	6
History of dementia	0	4	11

6.8. Summary of results

Cognitive decline and stroke are closely related. This study has given a crude indicator of the prevalence of pre-existing and new-onset cognitive decline, and its associated risk factors. Using data from LATCH COG, I found that roughly 1 in 4 (23%) patients had cognitive decline prior to their ICH. Forty-one patients (10%) had cognitive impairment with no dementia. Fifty-two patients met the criteria for pre-existing dementia (13%).

In univariate analysis, CT neuroimaging markers of cerebral amyloid angiopathy and small vessel disease were associated with pre-existing cognitive decline (lobar ICH location, anterior and posterior white matter lesions, central (deep) atrophy score, CT composite SVD score and Edinburgh CAA criteria (CT only)). Increasing age, modified Rankin score (level of dependency) and haemorrhage volume were also associated with pre-existing cognitive decline.

In logistic regression analysis, patients who had a lobar ICH were twice as likely to exhibit pre-existing cognitive decline and 3 times more likely to exhibit pre-existing dementia than those who had a non-lobar ICH. Patients with central (deep) atrophy were over 4 times more likely to exhibit cognitive decline and 8 times more likely to exhibit dementia before their stroke than those without. In line with this, severity of white matter changes was associated with pre-existing dementia. Patients with a compositive SVD score >0 (suggesting they have at least one feature of SVD) were over twice as likely to have pre-existing dementia, suggesting a neurodegenerative process. Increasing age and larger haemorrhage volume were also associated with increased likelihood of patients having pre-existing cognitive decline and dementia.

During the first 5 years of follow-up of LATCH COG, of the 168 patients who survived longer than 30-days after their ICH, 47 patients developed new-onset cognitive decline (cognitive impairment and dementia). Cumulative survival rates for patients remaining free of cognitive decline were 82% in the first year and reached 65% at 5 years. Cumulative survival rates for patients remaining free of dementia were 95% in the first year after ICH and 84% after 5 years.

In univariate analysis of LATCH COG, presence of posterior white matter lucencies was associated with new-onset dementia, indicating an association with markers of small vessel disease. In Cox regression analysis, patients who had a lobar ICH were twice as likely to exhibit new-onset cognitive decline than those who had a non-lobar ICH. In those who survived past 30 days, the incidence of new-onset cognitive decline was 37% in patients with lobar ICH and 20% in patients with non-lobar ICH.

When the IQCODE was compared to medical records for the detection of pre-existing cognitive impairment or dementia, in patients with an IQCODE score indicative of cognitive impairment, 73% had no record of cognitive impairment on their medical/GP records. In patients with IQCODE score indicative of dementia, 19% had no record of cognitive decline and 29% as having cognitive impairment (without dementia).

Due to the retrospective design of this study, it is likely that I have given a conservative estimate of the frequency of cognitive decline. This study was therefore followed-up with a prospective observational cohort study (LINCHPIN COG).

7. Methodology: LINCHPIN COG

I set up a prospective, population-based cohort sub-study in adults with first-ever ICH from LINCHPIN. Participants were given the opportunity to have their cognition and functional outcomes assessed at 6 and 12-24 months after their stroke. I measured pre-existing cognitive decline using the IQCODE informant questionnaire, and collected basic demographic data, vascular risk factors, stroke severity, level of dependency, and neuroimaging features on computed tomography and magnetic resonance imaging. The primary outcome was new-onset cognitive impairment (defined as MoCA score <26) at 6 months, when I also measured functional outcomes (depression, fatigue, health-related quality of life). This chapter includes a detailed discussion of the method used to collect and analyse data. Strengths and limitations are included at the end of this chapter to aid the reader in interpreting the generalisability and clinical implications of the findings.

7.1. Research objective and questions

The overall aim of LINCHPIN COG was to:

- Investigate the demographic, clinical, radiographic and functional outcomes associated with the occurrence of cognitive impairment following an ICH.

To meet this aim, the following research questions were developed:

1. What is the prevalence of pre-existing cognitive impairment and dementia in patients who have had their first-ever ICH?
2. What is the incidence of new-onset cognitive impairment in patients who have had their first-ever ICH at 6 months after their stroke? Is there a difference in cognitive assessment scores between 6 and 12-24 months?
3. How do the scores on MMSE, MoCA and ACE-III compare when assessing cognition in patients who have an ICH at 6 months after their stroke?
4. What factors (demographic, clinical and radiographic) are associated with new-onset cognitive impairment at 6 months in patients who have had an ICH?
5. Is cognitive impairment at 6 months correlated with assessments of functional outcome?

7.2. Selection of participants

Participants were included in LINCHPIN COG if they met the inclusion criteria outlined in Box 16.

Box 16: LINCHPIN COG inclusion criteria

Participants were eligible if they were:

- Diagnosed as having first-ever 'primary' ICH (not secondary to an underlying tumour, intracranial vascular malformation or venous thrombosis etc):
ICH was defined as the abrupt symptomatic onset of severe headache, altered level of consciousness, or focal neurological deficit, anatomically referable to a focal collection of blood within the brain parenchyma as observed on brain imaging (by a neuroradiologist with an interest in stroke) or at autopsy, which was not attributable to prior trauma or haemorrhagic conversion of a cerebral infarction
- Adults, aged 18 or over at time of diagnosis
- Seen as an inpatient or neurovascular outpatient at Western General Hospital, Royal Infirmary Edinburgh or St John's Hospital
- Resident in the NHS Lothian healthboard region
- Diagnosed with ICH between August 2014- July 2016

Participants were excluded from LINCHPIN COG if they met any of the exclusion criteria outlined in Box 17.

Box 17: LINCHPIN COG exclusion criteria

Participants were excluded if they had:

- ICH definitely attributable to trauma
- Exclusively extra-axial intracranial haemorrhage (i.e. subarachnoid, subdural, or extradural). However, patients with intraparenchymal haemorrhage that extended into other compartments could be included

- ICH into a tumour, from a proven intracranial vascular malformation, due to venous sinus thrombosis, or which proves to be a haemorrhagic transformation of a cerebral infarction after further imaging or autopsy.
- Refused consent to LINCHPIN

7.3. Methods

Participants were recruited from the ethically approved LINCHPIN study, which was a prospective cohort study examining the causes of ICH using clinical assessments, brain MRI, blood samples and research autopsy in case of death. Eligible participants were approached by a member of the LINCHPIN research team before, or soon after, hospital discharge (or later, if that was more appropriate for the patient) to ascertain whether they would be interested in participating in the study. The participant or nearest relative were given an information leaflet and time to consider the study and ask any questions that they may have before signing a consent form.

Six-month survivors who had consented to participate in LINCHPIN were given the opportunity to take part in a more detailed assessment of their cognition and functional outcomes at 6 and 12-24 months after their stroke. This part of the study ran for three years, from March 2015-February 2018 inclusive. LINCHPIN participants were approached with a separate consent form and information leaflet at 6 months post-ICH (see Appendix 7 and 8). Where possible, patients were also followed-up at 12-24 months after the index ICH.

I assessed the suitability of LINCHPIN research participants for this sub-study by contact with them or their nearest relative, where I offered them the opportunity to be assessed at home if preferred. I believed that it was important to include those patients who were unable to be assessed in a clinic setting because their cognitive function may be more severely affected, and not including them in the study would bias the assessment of cognitive function after ICH.

Consent was sought from patients for the assessments outlined in the Schedule of Evaluations (Table 23 and 24; Appendix 9: LINCHPIN COG participant assessments). Participants were assessed in a structured, face-to-face interview, lasting approximately 60-90 minutes.

Table 23: Schedule of evaluations for those with mental capacity

Assessment	Visit 1: 6 months post-ICH	Visit 2: 12-24 months post-ICH
Informed Consent Form	X	
Patient Demographics	X	X
EuroQOL-5D	X	X
Patient Health Questionnaire-2 (PHQ-9 if relevant)	X	X
SF-36 vitality scale	X	X
Clinical Dementia Rating scale	X	X
National Adult Reading Test	X	
ACE-III	X	X
MMSE	X	X
MoCA	X	X
NIHSS	X	X

Table 24: Schedule of evaluations for those without mental capacity

Assessment	Visit 1: 6 months post-ICH	Visit 2: 12-24 months post-ICH
Informed Consent Form	X	
Patient Demographics	X	X
EuroQOL	X	X
Clinical Dementia Rating scale	X	X
NIHSS	X	X

7.4. Measures

7.4.1. Cognitive Assessment

There is no ideal way of assessing cognition after stroke. Many patients may not be able to participate in a full neuropsychological assessment covering all cognitive domains and screening tools such as the MMSE may miss subtle cognitive decline and dementia (Pendlebury and Rothwell 2009).

When performing quantitative assessments of cognition, the assessment tools differed according to the patient's mental capacity (see Tables 23 and 24 for further details). To measure the occurrence of cognitive impairment in participants, the following assessment tools were selected:

- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)
- Clinical Dementia Rating Scale (CDR)
- Addenbrooke's Cognitive Examination-III (ACE-III)
- Mini-Mental State Examination (MMSE)
- Montreal Cognitive Assessment (MoCA)

IQCODE

The systematic assessment of pre-existing cognitive impairment and dementia was conducted using the short version of the IQCODE (Jorm 1994). This questionnaire, which is rated by a close friend or relative, consists of 16 questions regarding the changes experienced by the patient over the last 10 years in aspects of daily behaviour requiring memory and other intellectual abilities. IQCODE scores between 53 and 63 were classified as cognitive impairment with no dementia, and pre-existing dementia was recorded as an IQCODE score of 64 and above (Jorm 1994).

Clinical Dementia Rating Scale

The Clinical Dementia Rating (CDR) scale is a staging instrument for dementia and has good reliability when used by non-physicians (McCulla et al, 1989). In a recent systematic review of clinical staging scales, the CDR scale was recognised as the best-evidenced scale in terms

of its reliability and validity (Rikkert et al, 2011). In a study looking at the validity of the CDR for the detection and staging of dementia, sensitivity for the detection of questionable dementia and actual dementia cases was 86% and specificity was 80% in relation to the gold standard (DSM III-R diagnostic criteria) (Chaves et al, 2007).

The Clinical Dementia Rating scale (CDR) was used to rate the level of cognitive impairment in all participants, both with and without mental capacity, as it is based on caregiver accounts of problems in daily functional and cognitive tasks (Morris 1993). The CDR scale allows the researcher to assess the level of cognitive impairment from none (0) to severe (3).

Patients with mental capacity were also assessed for cognitive impairment using the ACE-III, MMSE and MoCA.

Addenbrooke's Cognitive Examination

In a review by Pendlebury et al (2012), the Addenbrooke's Cognitive Examination–Revised (ACE-R), which included the MMSE, was recommended as a useful tool for measuring cognition in the stroke population.

The ACE-R is a brief test that assesses five cognitive domains: attention/orientation, memory, verbal fluency, language and visuospatial abilities. The total score is out of 100, with higher scores indicating better cognitive functioning. In the review mentioned above, sensitivity and specificity were optimal for mild cognitive impairment with a cut-off score of less than 94 (sensitivity 83% and specificity 73%). In a further systematic review looking at the accuracy and clinical utility of the ACE-R, the evidence suggested that it can provide information on a range of cognitive domains and can differentiate well between those with and those without cognitive impairment (Crawford et al, 2012).

Copyright issues have meant that the ACE-R has now been discontinued. The successor to this well validated test, the ACE-III, is similar in style to the ACE-R and provides scores in five sub-domains. Although this test has not yet been validated for use with stroke patients, the results of a recent study provided objective validation of the ACE-III as a screening tool for cognitive deficits in Alzheimer's disease (Hsieh et al, 2013). In addition, total scores on the ACE-III are highly correlated to the ACE-R with similar specificity and sensitivity values for the

same cut-offs. In this study, the cut-off score of 94 was used for the detection of mild cognitive impairment, as recommended by Pendlebury et al (2012).

Mini-Mental State Examination

The MMSE is a brief screening tool for cognitive impairment and dementia (Folstein, Folstein and McHugh 1975). Although two recent reviews have highlighted the inability of the MMSE to detect mild cognitive impairment, when compared to the ACE-R and MoCA, the MMSE performed similarly in detecting multi-domain impairments among stroke patients (Pendlebury et al, 2012). Blake et al (2002) examined the sensitivity and specificity of the MMSE for detecting cognitive impairment after stroke. The study identified an optimum cut-off of <24, with good specificity (88%) and moderate sensitivity (62%). The MMSE takes approximately 10 minutes to administer and is scored out of 30.

Montreal Cognitive Assessment

The MoCA was developed as a quick screening tool for MCI and dementia and assesses the following cognitive domains: visuospatial/executive functioning, naming, memory, attention, language, abstraction, delayed recall and orientation. In a recent population-based study of transient ischaemic attack and stroke, the MMSE and MOCA were administered to patients at a 6-month follow-up (Webb et al, 2014). In this study, the MoCA picked up considerably more abnormalities than the MMSE.

The MoCA only takes 10 minutes to administer, with a total possible score out of 30. In a further publication from the study mentioned above, the MoCA was recommended as a screening tool for cognitive impairment, where sensitivity and specificity for cognitive impairment were optimal with a score of <26 (sensitivity 87% and specificity 63%) (Pendlebury et al, 2012). In a recent systemic literature review of the use of cognitive screening tools after stroke, five studies investigated the sensitivity and specificity of the MoCA. Of these five studies, four reported adequate levels of reliability and validity for the detection of cognitive impairment after stroke (Stolwyk et al, 2014).

7.4.2. Functional outcome

To determine the association between cognitive impairment and functional outcomes after intracerebral haemorrhage, the following questionnaires and assessments were used:

- EuroQOL (EQ-5D)
- Patient Health Questionnaire 2 (PHQ-2)
- Short Form-36 (SF-36) vitality scale
- National Institutes of Health Stroke Scale (NIHSS)

While the EuroQOL is a global measure of health-related quality of life, the PHQ-2 is a brief screening tool for depression. In order to assess levels of fatigue, the SF-36 vitality scale has been chosen as it consists of 4 questions and is well validated for use with stroke patients. To gain an indication of neurological outcome in all participants, the National Institutes of Health Stroke Scale was chosen.

EuroQOL-5D

Throughout the literature, a multitude of both generic and stroke specific QOL measures have been developed. Based on my review of the literature (Chapter 3), previous studies have tended to select the EQ-5D or SF-36 as a generic measure of health-related quality of life, with no clear preference for which tool should be used with stroke patients. Both tools appear to measure broadly similar domains of health and have qualitatively similar test-retest reliability (Dorman et al, 1998; Dorman, Dennis and Sandercock, 1999). Despite their similarities and usefulness, the SF-36 is substantially longer than the EQ-5D. In order to keep the burden to participants as low as possible, the EQ-5D has been selected due to its length and ease of use (Dorman et al, 1997). The EQ-5D provides a reliable assessment of HRQOL in the general population and has been well validated in patients with stroke (van Agt et al, 2004; Dorman et al, 1997).

In addition to a Visual Analogue Scale (VAS), which takes a score of 100 for perfect health and 0 for dead, the EQ-5D has 5 subscales that assess: mobility, self-care, usual activities, pain and anxiety/depression. Each of these domains is scored on five levels of severity: no problems; slight problems; moderate problems; severe problems; and unable. The EQ-5D utility score integrates the ratings of the five dimensions into a single score, calculated using

population-based preference weights for each subscale. In the present analysis, I used the weights obtained from the UK population. A utility score is calculated to express HRQOL quantitatively as a fraction of perfect health with a score of 1 representing perfect health, a score of 0 representing death, and negative scores representing health scores considered worse than death. When patients were not able to answer the questionnaire themselves, proxy responders such as a relative or caregiver, were asked to rate the patient's HRQOL. The EQ-5D has previously been validated for use in proxy responders (Dorman et al, 1997).

EQ-5D scores from the general population were used as reference data. The EQ-VAS population norm for the UK is 83 (age 75+ is 74) and the EQ-5D utility score is 0.856 (age 75+ is 0.734) (Janssen and Szende 2014). As the data on the EQ-5D dimension are ordinal, information is often presented as the proportion of the population reporting problems on each level of severity, for each dimension. However, because the number of people reporting severe problems is usually very small in population surveys, it is common for results to be presented in a dichotomised fashion using categories 'no problems' and 'problems' for each of the dimensions (Janssen and Szende 2014). The population norms for the percentage of people in the UK (all ages) reporting problems within each of the 5 domains is as follows: Mobility 18%; Self-care 4%; Usual activities 16%; Pain/discomfort 33%; Anxiety/depression 21%.

PHQ-2/9

In a review which aimed to determine the accuracy of common screening tools in recognising depression in stroke patients, because the authors found no significant differences between measures, the Patient Health Questionnaire-2 (PHQ-2) was recommended as it is free and only has two items (Turner et al, 2012). The PHQ-2 enquires about the frequency of depressed mood over the past 2 weeks (Kroenke, Spitzer and Williams, 2003). The PHQ-2 score ranges from 0-6 and asks how often in the last 2 weeks the patient has been bothered by the following problems:

1. little pleasure or interest in doing things?
2. feeling down, depressed or hopeless?

While the construct and criterion validity make it an attractive measure for depression screening (Kroenke, Spitzer and Williams, 2003), a cut-off score of 2 or more has a sensitivity of 0.75 and specificity of 0.76 (de Man-van et al, 2012).

Although this two-item scale has psychometric support as a screening tool, those scoring 2 or more were administered a further 7 items, to complete the full 9-item version (de Man-van et al, 2012). The PHQ-9 discriminates well between participants with any versus no depressive disorder, as well as between participants with and without major depression. The PHQ-9 performs best with a cut-off score of 10 or more, with 91% sensitivity and 89% specificity for major depression, and 78% sensitivity and 96% specificity for any depression diagnosis (Williams et al, 2005).

SF-36 Vitality Scale

Fatigue was measured using the vitality component of the SF-36 (Ware et al, 1993). The SF-36 was chosen as it is a valid and reliable measure of poststroke fatigue (Mead et al, 2007) and consists of only 4 questions:

How much of the time during the past 4 weeks did you:

...have a lot of energy?

...have you felt full of life?

...did you feel worn out? and

...did you feel tired?

Participants choose from a five-point scale ranging from 'none of the time' to 'all of the time' for each of the questions. The latter two items are reverse coded prior to scoring. Scores range from 0-20, with higher scores indicating higher levels of fatigue. The SF-36 has well established internal consistency, reliability, content validity, construct validity, and criterion-related validity, having been tested in a variety of population samples (Ware et al, 1993).

National Institutes of Stroke Scale

In order to gain an indication of neurological outcome in all participants, I used the National Institutes of Health Stroke Scale. It only takes 10 minutes to administer and assesses severity of impairment in level of consciousness, ability to respond to questions and obey simple commands, papillary response, deviation of gaze, extent of hemianopia, facial palsy, resistance to gravity in limbs, plantar reflexes, limb ataxia, sensory loss, visual neglect, dysarthria and aphasia (Lyden et al, 1999). Items are graded on a 3- or 4-point ordinal scale where 0 means no impairment. Scores range from 0-42; where higher scores indicate greater severity. Stroke severity may be stratified based on NIHSS scores as follows: very severe >25; severe 15-24; mild to moderately severe 5-14; and mild 1-5 (Brott et al, 1989).

7.5. Patient Demographics and Medical History

Data were collected using a standardised proforma for all patients. Information recorded from the patient, their hospital records and primary care records included details of the clinical event, medications, basic demographics, significant co-morbidities occurring before the index ICH (specifically TIA and ischemic stroke) and pre-existing level of dependency (as rated by the modified Rankin scale). Participants were asked to fill out a brief questionnaire at 6 and 12-24 months post-ICH to determine whether there have been any changes to the above information.

7.6. Radiological Assessment

Brain CT scans were available for all patients on admission. At least one neuroradiologist evaluated CT images with a standardised pro forma derived from previous largescale stroke studies (Rodrigues et al, 2018). Using the CT scans, the following data were recorded:

- location of haemorrhage (lobar or non-lobar)
- haemorrhage volume
- presence or absence of old vascular lesions (lacunes)

- severity of anterior and posterior white matter lucencies (3-point rating scale with a higher score denoting more severe white matter lucencies (van Swieten et al, 1990))
- severity of central (deep) or cortical cerebral atrophy (3-point rating scale where a higher score denotes a more severe atrophy (Sato et al, 2016))
- composite SVD score (one point for each of the following: >1 lacune, severe white matter lucencies and severe atrophy)

7.6.1. Definition of lobar and non-lobar ICH

ICH location was defined as either 'lobar' or 'non-lobar'. At least one experienced consultant neuroradiologist reviewed diagnostic brain imaging and classified ICH location as 'non-lobar' if an adult had a single infratentorial ICH (located in the brainstem or cerebellum), a single supratentorial deep ICH (located in the basal ganglia, internal or external capsule or thalamus without extension to a lobar area), or multiple ICHs in solely non-lobar locations (either supratentorial deep or infratentorial). All other ICHs were 'lobar'.

7.6.2. Hematoma volume

Hematoma volume was calculated using the first CT brain scan after the adult's presentation with ICH using the ABC/2 method where: A is the largest diameter of ICH on in the axial plane (cm), B is the largest diameter at 90o to A on the same slice (cm), and C is the maximal cranio-caudal diameter (cm) (Newman 2007).

7.6.3. Composite CT SVD score

A team of researchers from the Third International Stroke Trial created an aggregate SVD score by summing white matter changes, lacunes, and brain atrophy scores. White matter changes were rated with the Van Swieten Scale, where the posterior (range 0-2) and anterior (range 0-2) scores were combined into a 5-point ordinal scale (0-4) (van Swieten et al, 1990). The presence and number of lacunes was recorded, and brain atrophy was defined as central (deep) or cortical and rated with a 3-point ordinal scale as none, moderate, or severe (Sato et al, 2016). One point was assigned for each of the following if present: severe lucencies (Van Swieten Scale = 2) in anterior or posterior white matter, lacunes >1, and

severe (=2) central or cortical atrophy. The combined 4-point ordinal score therefore assessed the global burden of SVD from 0 (no imaging features of severe SVD) to 3 (imaging features of SVD scored as severe for each imaging variable) (Arba et al, 2017).

7.6.4. Composite MRI SVD score

Participants recruited into the LINCHPIN study underwent a brain MRI at 3-6 months after their ICH. Participants were excluded if they had a contraindication to MRI (for example, a permanent pacemaker or metal implants) or were unable to tolerate MRI because they were too unwell, claustrophobic or unable to lie flat for the scan duration. MRI was done using a 1.5T MRI scanner. The scan protocol consisted of T1 sagittal sequences and the following axial sequences: T2-weighted, FLAIR and gradient echo. All brain scans were rated by at least one neuroradiologist with an interest in stroke. The neuroradiologist rated all scans for presence and number of lacunes, presence and number of cerebral microbleeds, white matter hyperintensities (deep and periventricular white matter hyperintensities were both coded according to the Fazekas scale from 0 to 3, with a higher score denoting more severe white matter lesions (Fazekas et al, 1987)), enlarged perivascular spaces in the basal ganglia (rated on a validated semiquantitative scale from 0 to 4, where 0= no enlarged perivascular spaces and 4= >40 enlarged perivascular spaces (Doubal et al, 2010)).

The total MRI burden of SVD was rated on an ordinal scale from 0 to 4, by counting the presence of each of the 4 MRI features of SVD (Staals et al, 2014). A point was awarded for each of the following: presence of lacunes and cerebral microbleeds were defined as the presence of one or more lacunes (1 point if present) or any cerebral microbleed (1 point if present). Presence of perivascular spaces was counted if there were moderate to severe (grade 2–4) perivascular spaces in the basal ganglia (1 point if present). Presence of white matter hyperintensities was defined as either deep white matter hyperintensities (Fazekas score 2 or 3) or periventricular white matter hyperintensities extending into the deep white matter (Fazekas score 3) (1 point if present).

7.7. Premorbid verbal IQ

The National Adult Reading Test (NART) was devised to predict premorbid intellectual functioning in people suspected of having dementia so that the extent of cognitive decline

could be assessed by comparing these results with current performances (Nelson 1982). The NART is one of the most widely used objective measures to estimate premorbid IQ and consists of a list of 50 words, each of which the participant must try and pronounce correctly. The NART was initially developed to assist in the estimation of premorbid IQ in dementia, as reading is considered to be an over-learned skill that can be maintained, despite deterioration in other areas of cognitive functioning. Essentially, this test enables clinicians to estimate an individual's level of intellectual functioning prior to the onset of injury. While other measures have become available, such as the Wechsler test of Adult Reading and the Test of Premorbid Functioning, the NART has maintained its relevance and clinical utility. Although the NART has not been assessed for use in a stroke cohort, studies have established its validity and reliability as a method of estimating premorbid IQ in clinical populations (Nelson and O'Connell 1978; O'Carroll and Gilleard 1986; Crawford, Parker and Besson 1988).

7.8. Feedback

After meeting with the RUSH patient reference group, it was decided that the option should be available for participants to receive written feedback with the results of their assessment (Appendix 10). Such feedback gave an indication of the cognitive areas that were impaired, as well as those that remained intact (Bisikier and Bickerton 2013). Participants were given my contact details and asked to contact myself or their GP if they had any queries or concerns regarding this feedback.

7.9. Reporting Results to GP

Consent was sought from all participants to contact their GP with a summary of the cognitive and functional outcome assessment results. Having a record of the test results in all participants' medical files could allow for a comparison to be made if they needed to be re-assessed at some time in the future.

7.10. Statistical Analysis

SPSS statistical software was used to conduct statistical analyses. The analysis of data were carried out separately for each of the research questions as outlined below.

1. What is the prevalence of pre-existing cognitive impairment and dementia in patients who have had their first-ever ICH?

Using descriptive statistics, the prevalence of cognitive impairment with no dementia and pre-existing dementia was described with 95% confidence intervals (CI).

IQCODE scores between 53 and 63 were indicative of cognitive impairment with no dementia, and pre-existing dementia was recorded as an IQCODE score of 64 and above (Jorm 1994).

2. What factors are associated with pre-existing cognitive impairment and dementia in patients who have had an ICH?

To determine whether there were any differences between patients with and without pre-existing cognitive decline (cognitive impairment or dementia), baseline characteristics and 6 month cognitive and functional outcome assessment scores were compared using the chi-square test for categorical variables and the Mann-Whitney U-test for continuous variables. Continuous data are reported as medians and inter-quartile range (IQR). Categorical data are presented as frequencies and percentages.

2. What is the incidence of new-onset cognitive impairment in patients who have had their first-ever ICH at 6 months after their stroke? Is there a difference in cognitive assessment scores between 6 and 12-24 months?

Using descriptive statistics, the incidence of new-onset cognitive decline was described with 95% confidence intervals (CI). Following the recommendations of Pendlebury et al (2012), sensitivity and specificity for cognitive impairment are optimal with MoCA <26 (sensitivity 87% and specificity 63%).

To assess whether there was a mean difference in cognitive assessment scores between 6 and 12-34 months, the Wilcoxin matched pairs test (the assumptions of normality were not met) was used.

3. How do the scores on MMSE, MoCA and ACE-III compare when assessing cognition in patients who have had an ICH?

Spearman's rank correlation was chosen to measure the strength of the association between the three cognitive assessments.

4. What factors (demographic, clinical and radiographic) are associated with new-onset cognitive impairment at 6 months in patients who have had an ICH?

To determine whether demographic, clinical or radiographic variables were associated with the occurrence of new-onset cognitive impairment (MoCA <26), univariate analysis was performed: chi-square test for categorical variables and the Mann-Whitney U-test for continuous variables (data were not normally distributed, as assessed by Shapiro-Wilk's test).

Continuous data are reported as medians and IQR and categorical data presented as frequencies and percentages. Missing data has been made explicit when presenting results and has only occurred for those participants who were not able to undergo an MRI scan.

The following variables include known predictors of cognitive decline for stroke patients and the elderly population in general and were used for univariate analysis (Baumgart et al, 2015; Zulkifly et al, 2016):

Clinical/demographic variables: age, sex, pre-ICH hypertension, pre-ICH diabetes, atrial fibrillation, previous ischaemic stroke or TIA, dependent before ICH (modified Rankin ≥ 2)

Radiographic variables: ICH location (lobar or non-lobar), haematoma volume, presence of old vascular lesions, white matter lucencies score, cortical atrophy score, central atrophy score, composite SVD score (CT) and composite SVD score (MRI)

5. Is cognitive decline at 6-months correlated with assessments of functional outcome?

Analysis was conducted to determine whether new-onset cognitive impairment was associated with measures of functional outcome 6 months post-ICH. The variables selected for this part of the analysis were as follows: SF-36 vitality scale, PHQ-9, EQ-5D utility score, EQ-5D VAS, EQ-5D mobility sub-score ≥ 1 , EQ-5D usual activities sub-score ≥ 1 , EQ-5D self-help sub-score ≥ 1 , EQ-5D pain/discomfort sub-score ≥ 1 and EQ-5D anxiety/depression sub-score ≥ 1 (for EQ-5D sub-scores: No problems = 0; Problems ≥ 1).

Mann-Whitney U-Tests were run to determine whether there was difference in scores on the SF-36 vitality scale, PHQ-9, EQ-5D utility and EQ-5D VAS between those with and without new-onset cognitive impairment. To determine whether there was a difference in distributions between the categorical variables (EQ-5D sub-scores) and the two cognitive status groups (those with or without new-onset cognitive impairment), a Chi-squared test was conducted.

7.11. Strengths and limitations

Strengths of the study include its prospective, population-based design with multiple overlapping sources of case ascertainment and comprehensive data collection. I examined exclusively a cohort of ICH patients and used detailed and standardised data collection, including the use of an established tool for evaluation of pre-existing and new-onset cognitive decline. A major strength is the detailed neuroimaging description of markers of SVD in the context of pre and post-ICH cognitive decline, including MRI investigations, with few missing data.

In this study, I chose to focus on cognitive decline instead of dementia as cognitive decline includes all cognitive consequences of stroke, even if criteria for dementia are not met. I chose an interval of 6 months after stroke for neuropsychological testing to avoid interference with unstable neurological conditions that are extremely frequent in severe strokes such as ICH. This design also increased the number of participants able to attend the follow-up clinic and undergo testing. One of the limitations is the use of the MoCA as an outcome measure. The MoCA is a rather crude measure of cognition and may lack sensitivity to vascular cognitive impairment. Nevertheless, the MoCA is a widely accepted test for the evaluation of cognition in elderly patients and is easily obtainable, thus maximising the number of patients with available data.

A limitation is that recruitment of patients was not fully consecutive because participation was dependent on informed consent, therefore involving a selection bias. In addition, patients with severe aphasia or those who were severely disabled/bedbound were not included in the analysis as they were unable to complete the neuropsychological tests. As a result, I might have slightly underestimated the number of patients who developed new-onset cognitive impairment. However, I did try to be as inclusive as possible to avoid the

effect of baseline selection criteria on the post-ICH cognitive impairment rates; only excluding 3 participants without any cognitive assessment (Pendlebury et al, 2015).

I acknowledge that the study size is small, therefore the results should be interpreted cautiously. I used a generic measure of HRQOL, designed to measure health-related quality of life outcomes for any disease, as opposed to stroke specific dimensions. Although the EQ-5D has been shown to be a valid measure of HRQOL after stroke, the instrument may nevertheless not reveal the full spectrum of symptoms and impairments associated with stroke, including psychological complications.

8. Results: LINCHPIN COG

8.1. Study population

Of the 48 participants with spontaneous intracerebral haemorrhage who were recruited to LINCHPIN COG between March 2015 and February 2018 I excluded 3 participants without any cognitive assessment (two were confined to bed and severely cognitively impaired with a severe Clinical Dementia Rating (CDR) score, and the other had severe aphasia with a questionable CDR score). The study population at 6 months therefore consisted of 45 participants (19 females; 42%; 95% CI 28-58%) with a median age of 72 years (interquartile range 54-79), all of which had available CT data from the time of their index ICH. Twenty-one participants had a lobar haemorrhage (47%; 95% CI 32-62%) and 24 participants had a non-lobar haemorrhage (53%; 95% CI 38-68%).

8.2. Prevalence of pre-existing cognitive impairment and dementia

To assess the prevalence of pre-existing cognitive decline, the IQCODE was used. IQCODE scores between 53 and 63 were indicative of cognitive impairment with no dementia, and pre-existing dementia was recorded as a score of 64 and above. Ten participants (22%, 95% CI 11 to 37) met the criteria for pre-existing cognitive decline (cognitive impairment or dementia). Of those ten, 8 participants (18%; 95% CI 8-32%) had cognitive impairment with no dementia and 2 met the criteria for pre-existing dementia (4%; 95% CI 1-15%). The prevalence of pre-existing cognitive decline was 24% among participants with a lobar haemorrhage (5 participants; 95% CI 8-47%) and 21% among participants with a non-lobar haemorrhage (5 participants; 95% CI 7-42%).

A comparison of characteristics between participants with and without pre-existing cognitive decline can be found in Table 25. According to the scale of variances, differences in clinical as well as functional outcome and imaging features between the two groups were compared using bivariate analyses: Pearson Chi-square test or Mann-Whitney U-test where appropriate (data were not normally distributed, as assessed by Shapiro-Wilk's test). Before comparing differences in medians with the Mann-Whitney U-Test, a visual inspection of distributions was made to ensure that the dependent variable had similarly shaped distributions across both groups of the independent variable. When running the chi-square test, if any cells had an expected count of less than 5, a Fisher's exact test was applied. Continuous data are

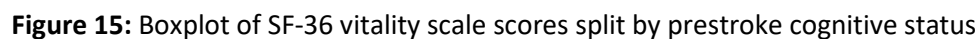
reported as medians and IQR. Categorical data are presented as frequencies and percentages.

Table 25: Characteristics of participants with and without pre-existing cognitive decline

	Pre-existing cognitive decline (n= 10) (%)	No pre-existing cognitive decline (n= 35) (%)	<i>p</i>
<i>Demographics and medical history</i>			
Age ^a	79 (68-83)	68 (52-77)	.061
Female sex	5 (50%)	14 (40%)	.720
Hypertension	6 (60%)	24 (69%)	.710
Diabetes	0 (0%)	6 (17%)	.312
Atrial Fibrillation	2 (20%)	1 (3%)	.119
Previous ischaemic stroke or TIA ^b	4 (40%)	3 (9%)	.034
<i>Functional outcome</i>			
Prestroke modified Rankin ≥ 2 ^b	2 (20%)	1 (3%)	.119
PHQ-9 ^a	3.5 (1-15)	0 (0-1)	.008
SF-36 vitality scale ^a	14 (9-15)	11 (9-13)	.050
EQ-5D utility score ^a	.55 (.42-.75)	.74 (.55-.84)	.171
EQ-5D VAS ^a	70 (67-80)	80 (70-90)	.099
IQCODE ^a	59 (55-63)	48 (48-48)	<.001
MoCA ^a	22 (18-27)	27 (21-28)	.065
NART errors ^a	14 (6-21)	14 (9-21)	.550
<i>Radiological data</i>			
ICH Location ^b			1.00
Lobar	5 (50%)	16 (46%)	
Non-lobar	5 (50%)	19 (54%)	
Haematoma volume (ml) ^a	9 (1-17)	18 (2-28)	.118
Old vascular lesions ^b	5 (50%)	9 (26%)	.244
White matter lucencies score ^a	4 (1-4)	1 (0-3)	.041
Cortical atrophy score ^a	1 (0-1)	1 (0-1)	.619
Central atrophy score ^a	1 (1-2)	0 (0-1)	.004
CT composite SVD score ^a	1 (1-2)	0 (0-1)	.035
MRI composite SVD score ^{ac}	2 (1-4)	2 (1-3)	.186

^aMedian (interquartile range); ^bFisher's Exact test applied; ^c Missing data for 5 participants

Figure 14: Boxplot of PHQ-9 scores split by prestroke cognitive status



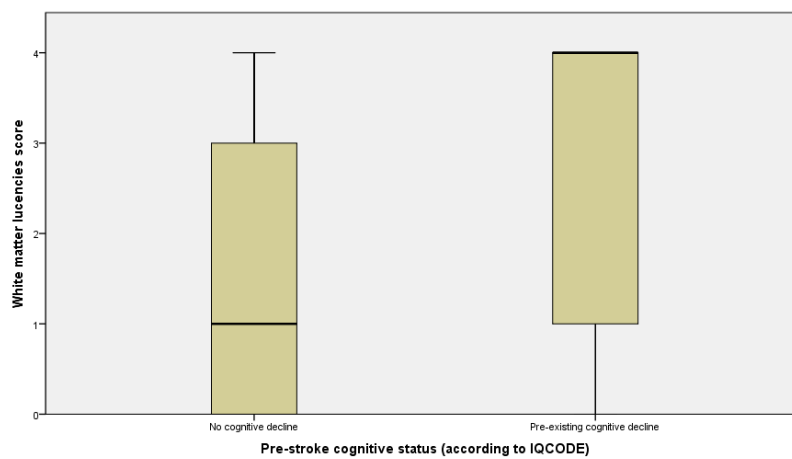


Figure 17: Boxplot of central atrophy scores split by prestroke cognitive status

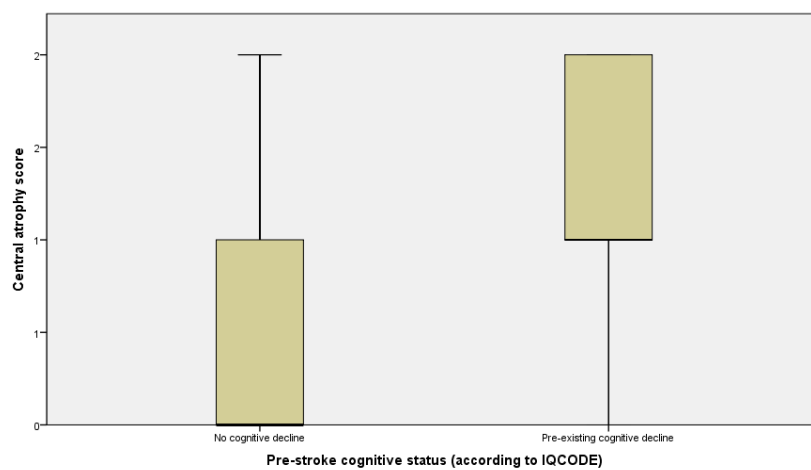
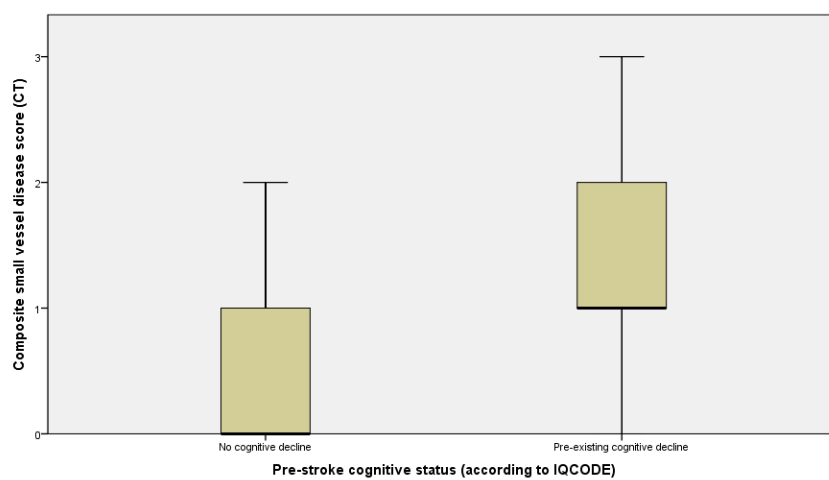
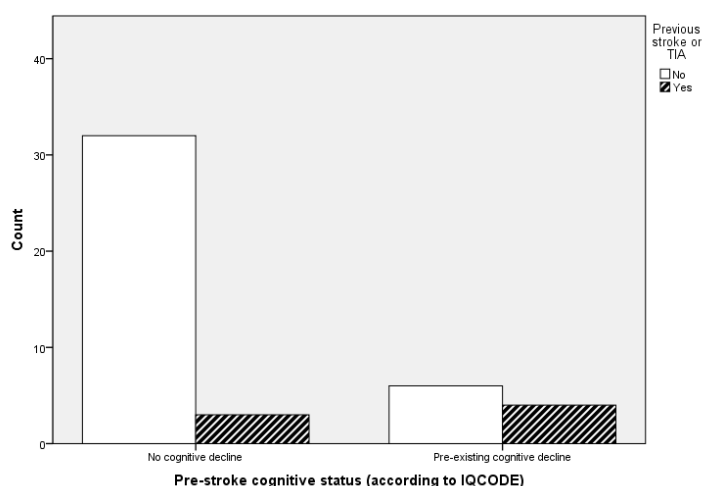


Figure 18: Boxplot of composite SVD scores (CT) split by prestroke cognitive status



Among the categorical variables, the only statistically significant result was found in participants who had had a previous ischaemic stroke or TIA ($\chi^2(1) = 5.849$; $p = .034$) (Figure 19). There was a moderate effect size, where Cramer's $V = .36$.

Figure 19: Bar chart of the number of previous strokes or TIAs in participants with prestroke cognitive decline versus those without



When conducting multiple analyses on the same dependent variable, the chance of committing a Type I error (rejecting the null hypothesis when you should not) increases, thus increasing the likelihood of observing a significant result by pure chance. To correct for this, or protect from Type I error, a Bonferroni correction was applied. The new p-value was the alpha-value ($\alpha_{\text{original}} = .05$) divided by the number of comparisons (22): ($\alpha_{\text{altered}} = .05/22$) = .002. To determine if any of the 22 comparisons was statistically significant, the p-value must have been $p \leq .002$. Therefore, in bivariate analysis (with a Bonferroni corrected significance level of $p \leq .002$), pre-existing cognitive decline at 6 months was the only variable associated with IQCODE ($p < .000$)

8.3. Incidence of new-onset cognitive impairment

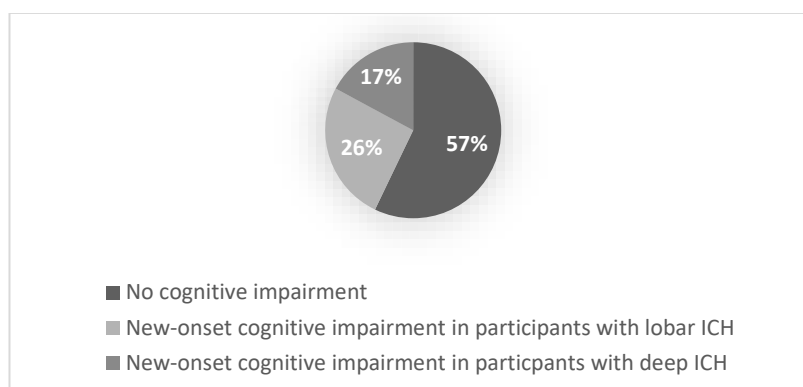
New-onset cognitive impairment is defined as cognitive impairment that was present after the ICH but was not present beforehand (as assessed by IQCODE). Of the 45 participants, 10 were therefore excluded from this part of the analysis due to pre-existing cognitive impairment or dementia. The study population for this part of the analysis is therefore 35 participants (14 [40%] are female), with a median age of 68 years (IQR 52-77). Sixteen

participants had a lobar haemorrhage (46%; 95% CI 29-63%) and 19 participants had a non-lobar haemorrhage (54%; 95% CI 37-71%).

The MoCA has been chosen as the screening tool of choice following the recommendations of Pendlebury et al (2012). Although the MoCA and ACE-III both had good sensitivity and specificity for detecting mild cognitive impairment in the stroke population, the MoCA takes less time to administer and was completed in full by more participants in the study. For screening purposes, sensitivity and specificity for cognitive impairment are optimal with MoCA <26 (sensitivity 87% and specificity 63%) (Pendlebury et al 2012).

Of the 35 participants without pre-existing cognitive decline, fifteen developed new-onset cognitive impairment, for an incidence of 43% (95% CI 26 to 61) at 6 months after ICH. The incidence of new-onset cognitive impairment was 6/16 (38%, 95% CI 15 to 64) after lobar ICH and 9/19 (47%, 95% CI 24 to 71) after non-lobar ICH (Figure 20).

Figure 20: New-onset cognitive impairment



8.3.1. Difference in cognitive assessment scores between 6 and 12-24 months

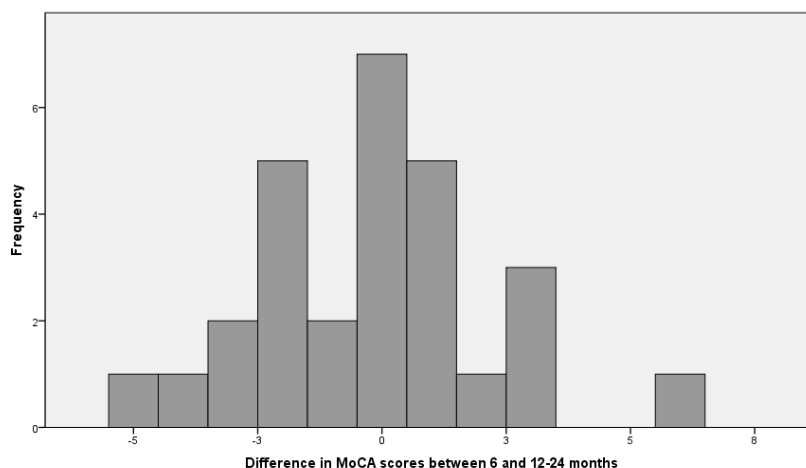
To assess whether there was a median difference in cognitive assessment scores between 6 and 12-24 months, the Wilcoxin matched pairs test was chosen. Although the difference in MoCA scores between the two periods of time was normally distributed (as assessed by Shapiro-Wilk's test, $p = .525$), an outlier was detected that was more than 1.5 box-lengths from the edge of the box in the boxplot, which meant that the assumptions of the paired-samples t-test were not met.

Of the 35 participants without pre-existing cognitive decline, 28 had two sets of cognitive results (at 6 and 12-24 months) and were therefore included in this part of the analysis. Of

the 28 participants, 10 showed an improvement in their MoCA score, 11 participants showed a decline in their cognitive score and 7 experienced no change (Figure 21).

A Wilcoxin matched pairs test determined that there was no statistically significant difference in median MoCA scores between 6 (score 26) and 12-24 (score 27) months ($z = -.561$, $p = .575$).

Figure 21: Difference in MoCA scores between 6 and 12-24 months



8.4. Comparing scores on MMSE, MoCA and ACE-III

Spearman's rank correlation was run to measure the strength of the association between the three cognitive assessments. Preliminary analysis showed the relationships to be monotonic, as assessed by visual inspection of scatterplots. There were positive correlations between all three assessments however, the strongest relationship was between the MoCA and ACE-III, which is in agreement with the findings of Pendlebury et al (2012) (Table 26).

Table 26: Correlation matrix for cognitive assessments

		MMSE	MoCA	ACE-III
MMSE	r_s	1.00	.651	.793
	p		<.001	<.001
MoCA	r_s	.651	1.00	.833
	p	<.001		<.001
ACE-III	r_s	.793	.833	1.00
	p	<.001	<.001	

8.5. Factors associated with new-onset cognitive impairment

To determine whether demographic, clinical or radiographic variables were associated with the occurrence of new-onset cognitive impairment, univariate analysis was performed: Pearson Chi-square test or Mann-Whitney U-test where appropriate (data were not normally distributed, as assessed by Shapiro-Wilk's test).

Before comparing differences in medians with the Mann-Whitney U-Test, a visual inspection of distributions was made to ensure that the dependent variable had similarly shaped distributions across both groups of the independent variable. When running the chi-square test, if any cells had an expected count of less than 5, a Fisher's exact test was applied. For those variables where a statistically significant difference was shown, the effect size was calculated. Continuous data are reported as medians and IQR. Categorical data are presented as frequencies and percentages.

In univariate analysis (with a Bonferroni corrected significance level of $p \leq .003$), new-onset cognitive impairment at 6 months was associated with pre-ICH history of hypertension ($p < .001$) (Figure 22 and Table 27).

Figure 22: Pre-ICH history of hypertension

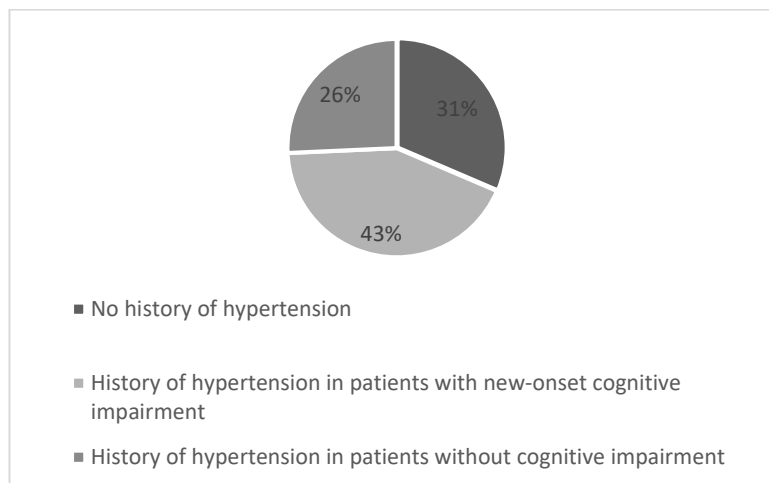


Table 27: Factors associated with new-onset cognitive impairment

	Participants with new-onset cognitive impairment (n= 15)	Participants without cognitive impairment (n= 20)	<i>p</i>
<i>Demographics</i>			
Age ^a	72 (58-80)	68 (48-76)	.27
Female sex	5 (33%)	9 (45%)	.49
<i>Vascular risk factors</i>			
Hypertension ^b	15 (100%)	9 (45%)	<.001
Diabetes ^b	4 (27%)	2 (10%)	.37
<i>Medical history</i>			
Atrial fibrillation ^b	1 (7%)	0 (0%)	.43
Previous ischaemic stroke or TIA ^b	3 (20%)	0 (0%)	.07
<i>Functional status</i>			
Dependent before ICH (modified Rankin \geq 2) ^b	1 (7%)	0 (0%)	.43
<i>Radiological data</i>			
ICH location			.56
Lobar ICH	6 (40%)	10 (50%)	
Non-lobar ICH	9 (60%)	10 (50%)	
Haematoma volume (ml) ^a	19 (5-39)	10 (2-26)	.31
Presence of old vascular lesions ^b	7 (47%)	2 (10%)	.02
White matter lucencies score ^a	3 (1-4)	0 (0-2)	.01
Cortical atrophy score ^a	1 (0-1)	1 (0-1)	.73
Central atrophy score ^a	0 (0-1)	0 (0-1)	.31
CT composite SVD score ^a	1 (0-2)	0 (0-0)	.01
MRI composite SVD score ^{a,c}	2 (2-3)	1 (0-2)	.04

^aMedian (interquartile range); ^bFisher's Exact test applied; ^cMissing data for 2 participants

8.6. Correlation of cognitive impairment with assessments of functional outcome

Analysis was also conducted to determine whether cognitive impairment after ICH was associated with measures of functional outcome. The variables selected for this part of the analysis were as follows: SF-36 vitality scale, PHQ-9, EQ-5D utility score, EQ-5D VAS, EQ-5D mobility sub-score, EQ-5D usual activities sub-score, EQ-5D self-help sub-score, EQ-5D pain/discomfort sub-score and EQ-5D anxiety/depression sub-score (for EQ-5D sub-scores: No problems = 0; Problems ≥ 1).

Mann-Whitney U-Tests were run to determine whether there was a difference in scores on the SF-36 vitality scale, PHQ-9, EQ-5D utility and EQ-5D VAS between those with and without new-onset cognitive impairment. Distribution of all scores were similar across both groups, as assessed by visual inspection. An exact sampling distribution has been used for U (Dineen and Blakesley 1973).

Median SF-36 vitality scale scores for those with (12) and without (11) cognitive impairment were not significantly different, $U = 157$, $z = .235$, $p = .831$.

Median PHQ-9 scores for those with (0) and without (0) cognitive impairment were not significantly different, $U = 147.5$, $z = -0.95$, $p = .934$.

Median utility scores for those with (.74) and without (.75) cognitive impairment were not significantly different, $U = 150.5$, $z = 0.17$, $p = 1.00$.

Median VAS scores for those with (85) and without (80) cognitive impairment were not significantly different, $U = 165.5$, $z = .521$, $p = 1.610$.

To determine whether there was a difference in distributions between the categorical variables (EQ-5D sub-scores) and the two cognitive status groups (those with or without new-onset cognitive impairment), a Chi-squared test was conducted. If any cells had an expected count of less than 5, a Fisher's exact test was applied. I could not detect statistically significant associations between new-onset cognitive impairment and any of the EQ-5D sub-scores at 6 months (Table 28).

Table 28: Associations between new-onset cognitive impairment and functional outcome at 6 months after ICH

	Participants with new-onset cognitive impairment (n= 15)	Participants without cognitive impairment (n= 20)	<i>p</i>
EQ-5D usual activity score ≥ 1	10 (67%)	8 (40%)	.12
EQ-5D self-help score ≥ 1	8 (53%)	7 (35%)	.28
EQ-5D mobility score $\geq 1^b$	12 (80%)	12 (60%)	.28
EQ-5D anxiety/depression score ≥ 1	7 (47%)	10 (50%)	.85
EQ-5D pain/discomfort score ≥ 1	6 (40%)	14 (70%)	.08
EQ-5D visual analogue scale ^a	85 (73-90)	80 (63-89)	1.61
EQ-5D utility score ^a	.74 (.57-.82)	.75 (.49-.84)	1.00
Depression (Patient Health Questionnaire-9) ^a	0 (0-1)	0 (0-1)	.93
Fatigue (Short Form-36 vitality scale) ^a	12 (9-14)	11 (9-13)	.83

^aMedian (interquartile range); ^bFisher's Exact test applied

8.7. Summary of results

Pre-existing cognitive decline affects one-fifth (22%) of patients with ICH (18% cognitive impairment and 4% dementia). For survivors of ICH without pre-existing cognitive decline, new-onset cognitive impairment is frequent with 43% of participants scoring <26 on the MOCA (indicating mild cognitive impairment) at 6 months.

Although not statistically significant after the application of the Bonferroni correction, those with pre-existing cognitive decline had lower mood (PHQ-9 score 3.5 v 0), lower EQ-5D utility scores (.55 v .74), lower scores on the EQ-5D VAS (70 v 80) and were more likely to be fatigued (SF-36 score 14 v 11) than those without pre-existing cognitive decline. Those with pre-existing cognitive decline also had higher white matter lucencies scores (4 v 1), higher central atrophy scores (1 v 0), were more likely to have had a previous ischaemic stroke or TIA (40% v 9%) and had a higher composite CT SVD score (1 v 0) than those without pre-existing cognitive decline.

43% of patients without pre-existing cognitive decline scored <26 on the MoCA at 6 months. Surprisingly, the incidence of new-onset cognitive impairment was higher among participants with non-lobar ICH. Between 6 and 12-24 months, 10 participants showed an improvement in MoCA score, 11 showed a decline and 7 experienced no change.

In univariate analysis of LINCHPIN COG, new-onset cognitive impairment at 6 months was associated with pre-ICH history of hypertension. This implies an important role of vascular processes. Cerebral blood vessels are the main target of the effects of hypertension on the brain. The resulting structural and functional cerebrovascular alterations underlie many of the neuropathological abnormalities responsible for the cognitive deficits, including white matter damage and brain atrophy.

Although not statistically significant, participants with new-onset cognitive impairment were more likely to have a previous ischaemic stroke or TIA (20% v 0%), presence of old vascular lesions (47% v 10%), a higher white matter lucencies score (3 v 0), a higher CT composite SVD score (1 v 0) and a higher MRI composite SVD score (2 v 1).

I could not detect statistically significant associations between new-onset cognitive impairment and functional outcomes at 6 months. The small sample size may have been a significant contributory factor, making it difficult to identify any statistically significant differences between those with and without cognitive impairment. Despite this, participants with new-onset cognitive impairment were more likely to have problems with usual activities (67% v 40%), require more self-help (53% v 35%) and have more problems with mobility (80% v 60%). These last three points in particular will now be explored in-depth in the qualitative interviews, where participants spoke about their inability to take part in activities that were integral to the pre-stroke lives, in addition to not being able to perform simple, everyday tasks.

9. Methodology: Qualitative interviews

To evaluate the experience of life after ICH with cognitive impairment, a simple qualitative study was embedded into LINCHPIN COG. Interviews were conducted with six LINCHPIN COG participants and four family members. It was hoped that by giving participant's and their family members the chance to tell their story, the impact that the ICH had on their lives could be explored to a level and depth that could not be easily or feasibly captured through quantitative means alone. This chapter includes a detailed description of the method used to collect and analyse data, and the measures taken to ensure quality. Strengths and limitations are included at the end of this chapter to aid the reader in interpreting the generalisability of findings.

Although the use of reporting checklists within qualitative research is debated, to help increase the reporting transparency, details about the researcher, study design, analysis and findings are summarised according to the consolidated criteria for reporting qualitative research (Tong, Sainsbury and Craig 2007; Appendix 11).

9.1. Research aim

The overall aim of the qualitative interview was to:

- Evaluate the experience of life after ICH with cognitive impairment.

This aim informed the research design and methods used, which will now be outlined in detail below.

9.2. Participants

9.2.1. Selection and recruitment of participants

Participants were selected from survivors of ICH who had previously consented to take part in LINCHPIN COG. A purposive sampling technique was employed to identify participants with

a range of residual cognitive impairments who could provide depth and diversity of responses relevant to the study (Patton 2002).

Participants were approached in the clinic or home setting by the researcher. They were informed about the study orally and asked for consent to have interviews audio recorded. Participants were initially recruited if they had their stroke 6-12 months prior to the interview. A design amendment later enabled inclusion of three participants who had their strokes 12-24 months prior to interview, to allow for the views of participants who were further along in their stroke journey.

Survivors were eligible if they suffered from communication problems (i.e. aphasia) if it did not limit their ability to reveal their subjective experiences. In four cases, a family member was present during the interview for which additional consent was sought. Family members added another perspective on the stroke experience.

Qualitative approaches usually aim to understand a relatively small number of participant's views. Due to the constraints of time inherent in a doctoral thesis, this study aimed to recruit five to eight participants who collectively represented a range of views. A total of six stroke survivors and four family members participated in the imbedded qualitative study and offered a range of characteristics. It was felt by myself and my supervisors that this was enough participants to address the research aim and offer an insight into the impact of living with cognitive impairment after stroke due to haemorrhage.

9.3. Methods

9.3.1. Data collection

Data were collected through individual face-to-face semi-structured interviews and took place between May 2016 and March 2018. Semi-structured interviews were the most appropriate method of collecting data as they allow a degree of consistency, whilst also allowing for exploration of particular issues of importance to respondents.

Qualitative interviewing encourages participants to tell their story of a particular experience, providing time and opportunity to share experiences. In this study, this meant interviewing around the specific episode of the participant's ICH and the time following it until the present

day. The interview schedule (Appendix 12) was developed with the assistance of colleagues and supervisors prior to the interviews. The first interview was a pilot for the interview schedule, where it was felt that the questions adequately covered the research areas of interest. Agreement of the core topics to be covered increased consistency; however, the relevance and clarity of the questions were constantly considered during the conduct of the interviews. In addition, the semi-structured nature of the interviews gave me scope to ask some spontaneous questions, where I could address participants' concerns and personal circumstances.

When I initially met with the participants, I stressed that they were under no obligation to participate and if they did agree to take part, they could withdraw at any time without providing an explanation. Once participants gave their informed consent, a convenient time and place for the interview was selected. Participants were given a choice of settings for the interview- in their own home or in a clinic setting- to make them most comfortable. All participants opted to have the interviews in their own home. The interviews themselves lasted between 45-90 minutes.

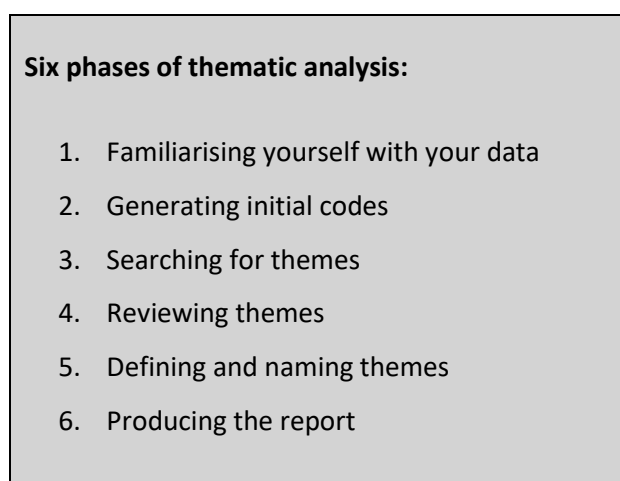
All interviews started with me asking the participants to describe what happened on the day of the stroke. This provided me with relevant background and allowed participants to describe their perception of events. Information was then sought on their experiences of life after stroke, services and support received and the impact of any residual cognitive impairments.

9.4. Transcription and analysis

All interviews except one were digitally recorded using encrypted software. Personal identifiers were removed through the use of a bleep censor, and each interview was given a number. Each interview was then transcribed verbatim in full, either by myself or a reputable third party that had been recommended by my supervisor. If the interview was transcribed by a third party, I read the transcripts for the interviews and listened to the digital recording in full to confirm reliability and accuracy. In the interview that was not digitally recorded (the participant did not wish to be recorded), field notes were taken. Transcribed interviews were not returned to the participants.

As this was the first study to explore life after stroke in a cohort solely comprised of patients with cognitive impairment following an ICH, it was decided that this research should focus on identifying themes within the participant's experiences. The most appropriate method of analysis was therefore a thematic analysis. Although this has been criticised for its lack of transparency, the analysis of the data followed the six phases of thematic analysis (Figure 23) as described by Braun and Clarke (2006). Although I lacked experience of qualitative analysis, I sought appropriate academic supervision and consulted worked examples of thematic analysis within other healthcare research (e.g. Cassol et al, 2018 and Frith and Gleeson 2004). Where possible, I followed the 15-point checklist of criteria for good thematic analysis including transcription, coding, analysis, and fulfilling the report (Braun and Clarke 2006) (Appendix 13).

Figure 23: Braun and Clarke's (2006) six phases of thematic analysis



The qualitative research software programme NVivo (Version 11) was used to support coding, management, and analysis of data. It helped simplify the process of data sorting and led to a more exhaustive analysis. An inductive step-by-step thematic analysis was carried out on all anonymised interview transcripts. This form of thematic analysis is data-driven, where the themes are strongly linked to the data themselves (rather than being driven by a theoretical interest). It is also important to note that themes were identified within the explicit meanings of the data (semantic). With this approach, although the researcher is not looking for anything beyond what a participant has said, the analytic process involves a process of interpretation, where there is an attempt to theorise the significance of themes and their broader meanings (Braun and Clarke 2006). In the presentation of findings,

verbatim quotations from interviews have been used. All quotations are from stroke participants unless labelled otherwise.

The first phase of thematic analysis is familiarisation with the data. I first became familiarised with the whole data set through repeatedly reading and reflecting on the transcripts and audio recordings. Writing was recognised as an integral part of the analysis and began in this first phase through the jotting down of ideas, initial concepts and recurring patterns or themes.

The second phase involved the production of initial codes from the data in a systematic fashion. Codes identify a feature of the data that appears interesting to the researcher. Although initial codes were manually written on the texts that were being analysed in phase one as part of the familiarisation process, coding was later performed using NVIVO 11. See Figure 24 for an example of codes applied to a short segment of data.

Figure 24: Data extract, with codes applied

Data extract	Code
<p>Everything's more of an effort [1].... So you kind of step back from what you were or what you done before [2]... 'Cause you don't want to be a burden on anybody [3]. I mean, we went away on holiday... and it was so hard 'cause I couldn't walk properly [4]. So I felt embarrassed [5]... Like even going down to the beach or going down to the pool... I was walking like Quasimodo, this limp, dragging my leg [4]... Ken, I just didn't feel right [6] and I felt insecure [7]... (Dawn)</p>	<ol style="list-style-type: none"> 1. Everything is harder 2. Taking a step back 3. Feeling like a burden 4. Physical impairment 5. Feeling embarrassed 6. Not feeling like the person they were before 7. Feelings of insecurity

Once the entire data set had been coded and collated, phase three involved the combining of codes into overarching themes that accurately depicted the data. According to Braun and Clarke (2006 p.82):

“a theme captures something important about the data in relation to the research question and represents some level of patterned response or meaning within the data set.”

This phase led to an initial list of themes and sub-themes.

In the fourth phase, I extracted and classified all quotations (i.e., phrases or paragraphs) that corresponded to one (or more) of the themes. During this phase, it became evident that some of the themes did not have enough data to support them, while other themes needed to be broken down into separate themes or sub-themes (for example, it was decided at this stage that ‘impact on family members’ had enough data supporting it to be a major theme, rather than being a sub-theme of ‘life after stroke’). This phase ended once all the themes had been reviewed and refined (see Box 18 for the final themes and sub-themes).

Box 18: Final themes and sub-themes

Themes	Sub-themes
The effects of stroke on sense of self and identity	<ul style="list-style-type: none"> • No longer felt like the person they used to be • Changes in ability to perform simple, everyday tasks • Not being able to engage in usual activities • Impact to working life • Impact of cognitive impairments
Adaptions and adjustment	<ul style="list-style-type: none"> • Ways of adapting to disability • Benefits of health services and resources • Help of social supports
Uncertainty	<ul style="list-style-type: none"> • Uncertainty during stroke onset • Uncertainty over course of stroke • Uncertainty about long-term recovery
Impact on family members	<ul style="list-style-type: none"> • Hospital admission: uncertainty about prognosis • After discharge: adjusting to life at home

The fifth phase included a comprehensive analysis to examine the extent to which the themes and sub-themes contributed to an understanding of the data. For each theme, all the included quotations were synthesised to bring out the main ideas. A summary was then produced for each theme using the content provided by the participants. In relation to each theme, I asked the question: 'So what?' in order to identify the key issues (Braun and Clarke 2006). All summaries were compared to eliminate duplication and to ensure that all the relevant data from each theme was being grouped together in a logical and meaningful way.

The sixth (and final) phase involved writing the findings and led to a detailed description of the results. To ensure validity, descriptive results were accompanied by rich and thick verbatim quotations to support the findings (Noble and Smith 2015).

9.5. Ensuring quality in qualitative research

It is important to consider the quality of qualitative research. As stated by Morse et al (2002, p.1):

"Without rigor, research is worthless, becomes fiction, and loses its utility."

Although the tests and measures used to establish the validity and reliability of quantitative research cannot be applied to qualitative studies, in the broadest context, these terms remain applicable. While validity refers to the appropriateness and application of the methods undertaken and the precision with which the findings accurately represent the data, reliability describes consistency within the chosen analytical procedures.

For the novice researcher, demonstrating rigour can be challenging as there is no accepted consensus about the standards by which qualitative research should be judged. Various authors have developed guidelines to facilitate researchers' when thinking about quality. Noble and Smith (2015) outline several strategies that qualitative researchers can adopt to ensure the credibility of their study findings, some of which are discussed below.

The first strategy suggested by Noble and Smith (2015), is accounting for biases (both personal and theoretical) which may have influenced the findings. The way to do this is by being reflexive:

“Reflexivity is an essential requirement for good qualitative research... [and] refers to the process of critically reflecting on the knowledge we produce, and our role in producing that knowledge” (Braun and Clarke 2014, p. 37).

Although I had taken an inductive approach to thematic analysis: a process of coding the data without trying to fit it into the researcher’s analytic preconceptions; researchers cannot free themselves of the theoretical context of their research.

Before interviewing participants, two pilot interviews were conducted, one with a lecturer of Nursing Studies from the University of Edinburgh and the other with a member of the RUSH patient representative group. Although I had prior experience of focus group interviewing, this was the first time that I would be carrying out in-depth semi-structured interview discussions. The pilot interviews were therefore a great opportunity to practice this style of interviewing. These sessions were particularly useful for teaching me to tolerate silence and to be careful not to use leading questions.

All the interviews were conducted by myself, a nurse who has previous knowledge and experience of working with older people who have cognitive impairments and dementia (Russell 1999). All potential participants were primed to the intended area of study (i.e. experiences of life after stroke) via the participant information sheets and through brief discussion. Prior to the qualitative interviews, I had met with participants on at least two previous occasions (e.g. during recruitment, clinic or MRI visits). I was careful not to use this pre-existing relationship to pressure people into participating in the qualitative study. It also meant having to be careful not to gloss over any relevant information during the interviews that was already known (Braun and Clarke 2014). I am also aware that analytic preconceptions may have been developed based on having worked with stroke patients as a student nurse and having developed a rapport with participants prior to the qualitative interviews. However, Lincoln and Guba (1985) describe building rapport and trust with participants prior to interview as a way of improving credibility. They suggest that by building a rapport with participants, the context of interviews will be appreciated, thus facilitating better understanding.

The second strategy outlined by Noble and Smith (2015) is to acknowledge any biases in sampling and ongoing critical reflection of methods to ensure enough depth and relevance of data collection and analysis. To enhance validity, detailed description is offered of the

sample, findings, data collection and analysis. Purposeful sampling involves the intentional selection of participants who can provide a richness or depth of information pertaining to the research question. Although there was potential for bias in selection, the aim was not to acquire a sample that was statistically representative of the population or to achieve generalisation (Palinkas et al, 2015). Instead, purposive sampling was employed for the identification and selection of information-rich cases for the most effective use of limited resources (Patton 2002). Initial analysis was conducted concurrently with data collection and informed the point at which data were deemed sufficient. Recruitment was therefore stopped when data sufficiency (rather than saturation) was achieved.

Noble and Smith (2005) also suggest including rich and thick verbatim descriptions of participant's accounts to support findings and engaging with other researchers to reduce research bias. Selected quotations from participants are included in the findings chapter to allow the reader to judge interpretations and credibility of the analysis. Although I carried out all of the analysis, themes were discussed with supervisors who had stroke and qualitative research expertise. Often referred to as 'peer debriefing', exploring the analysis and conclusions with a supervisor allowed for the development of additional perspectives and explanations at various stages of the process of data collection and analysis (Lincoln and Guba 1985).

9.6. Strengths and limitations

A strength of the present study was the use of a qualitative design with an inductive driven analysis. Thematic analysis made it possible to discover the most important themes from the material, and a semi-structured guide was used to ensure that I concentrated on specific topics related to the purpose of the study.

Participants talked at length in interview and rich data were collected. A strength of this study, particularly in relation to many other studies on stroke, is my inclusion of participants with expressive language problems. Although this created challenges as at times, particularly when participants struggled to explain what happened, with the help of family members, participants attempted to make sense of their stories.

Participants were selected purposively, and findings need to be interpreted in this context. This study is confined to patients who were resident in the Lothian region of Scotland, and this needs to be considered when the knowledge is transferred to other cultural contexts. Future studies should include patients and carers in other settings to compare experiences. The six stroke survivors and four family members recruited to this part of the study are unlikely to fully represent the diversity of people living or caring for those who have had a stroke due to haemorrhage.

A number of potential criticisms of this study surround the sample. The number of participants in this study was small: an increased number of interviews may have strengthened the study. However, because the aim of the interviews was not to reach data saturation, it was decided after six interviews that I had sufficient data to analyse in order to address the research aim.

There was an age and gender imbalance within the study. Only two out of the six stroke survivors were female, and none of the family members were male. In addition, the research specifically involved younger, higher functioning survivors of stroke. All participants in the qualitative interviews were below the average retirement age. As such, they may have experienced different types of losses than those who were older. To explore the impact of gender and age upon the experience of life after ICH, a larger and more diverse sample of stroke survivors and family members is required. However, to the researcher's knowledge, this is the first study to explore this phenomenon, it is therefore hoped that the findings will be of interest to those from similar populations.

A further potential criticism of the study relates to the lack of triangulation through member-checking, as there was no opportunity for participants to check their understanding or clarify meaning (Lincoln and Guba 1985). However, rather than representing a fixed truth, the interviews provide the reader with a snapshot of the participant's experiences of having had a stroke at one point in time. It is possible that events or reflections that occurred after the interviews could alter their story.

Although some findings have been reported on the impact of stroke on the lives of family members, that this was never the focus of the interviews. When planning the study, it had not been intended that interviews would be conducted in the presence of family members. The extent to which this altered the content and management of the interviews cannot be

known. However, all interviews were conducted by the same researcher, giving a level of internal consistency.

9.7. Introducing the participants

Of the six stroke survivors who were interviewed, two were female and four were male. Respondents were all in their 40s to 60s. Five of the survivors were married and one was recently widowed and lived with their sister. All respondents were experiencing some residual impairments from their stroke including weakness or paralysis on one side of the body, slurred speech, spatial and perceptual deficits, vision loss, aphasia, memory impairments, word finding difficulties, reduced speed of information processing and fatigue.

A brief introduction to each of the stroke survivors has been provided for the reader below. To preserve anonymity, some of the details have been changed. Each interview participant has been allocated a pseudonym. The severity of stroke is indicated by the National Institutes of Health Stroke Scale (NIHSS). Scores range from 0 to 42, with higher scores indicating more severe neurological deficits. Scores on the EQ-5D visual analogue scale have also been provided to give the reader a sense of how the stroke survivor perceived their own health.

9.7.1. Participant 1: Adam

Adam was a male in his 40s who lived with his wife and young children. He was a self-employed Software Developer who was studying for his MBA when he had the ICH. He had a left-sided lobar ICH. MRI did not reveal any underlying cause.

The participant was participating in a marathon on the day of the stroke. He had been feeling well on the day, but half-way through became dizzy and developed a right-sided weakness, hemianopia and aphasia. He spent 10 weeks recovering in hospital; the first 2 weeks was spent in an acute ward before he was moved to a rehabilitation facility.

Once home, the participant was very motivated about recovery and was participating in physiotherapy once every fortnight, exercised regularly at home and had recently started running again. At the time of interview, he was very keen to return to work. However, he still

had some slurred speech, difficulties with producing spoken language (comprehension remained intact) with a mild right-sided weakness. NIHSS score was 3 and EQ-5D VAS was 80.

9.7.2. Participant 2: Jim

Jim was a supermarket worker in his 50s who lived with his wife. The participant was working as a DJ at a local club when he developed a right-sided weakness and mixed receptive and expressive aphasia (difficulty with both comprehension and putting words together). He was very hypertensive at the time of the stroke and was admitted to hospital where a CT revealed a left-sided mixed lobar and non-lobar ICH.

Since this time, the participant had made a gradual recovery but was unable to return to work. He walked with one stick and was able to walk around the shops with occasional stops. He had noticed less of an improvement in his speech than his mobility and still clearly had problems with expressive and receptive functioning. His mood was fine on Fluoxetine and he slept well. He continued to be affected by central poststroke pain affecting the right-hand side of his body and was on regular pain relief. NIHSS score was 5 and EQ-5D VAS was 80.

9.7.3. Participant 3: Colin

Colin was a retired Enforcement Officer in his 60s who lived with his wife at the time of the stroke but who had subsequently died. His wife had found the participant collapsed on the toilet and CT revealed a left-sided non-lobar ICH with early hydrocephalus due to extension of the haemorrhage into the ventricles. The participant suffered from Type 2 diabetes and hypertension and scans showed he had a previous ischaemic stroke a few years earlier. The underlying cause for ICH was likely to be small vessel disease as the MRI revealed some non-lobar microhaemorrhages and signs of white matter disease.

After the stroke onset, the participant was transferred urgently to ITU for external ventricular drain and he gradually recovered on the stroke unit. Although he was a little fatigued after discharge, he had got back to his normal self and spent most days walking his dogs and watching television.

The participant's biggest concern was undergoing a driving assessment so he could regain his licence. Although he felt as if he had not been affected by the stroke, at the driving assessment he was found to have residual cognitive impairments, and it was decided that his medical condition was having an adverse impact on his ability to drive safely. NIHSS score was 0 and EQ-5D VAS was 90.

9.7.4. Participant 4: Helen

Helen was a business manager in her 50s who lived with her husband. She developed a sudden right homonymous hemianopia following two days of migrainous headache. She was admitted to hospital and CT revealed a left-sided lobar ICH. Shortly after admission, the participant's symptoms progressed, and her conscious level dropped. The participant needed ITU admission for intubation and ventilation after which she was noted to be dysphasic (impairment of speech and verbal comprehension) with a right-sided weakness. No underlying cause was revealed.

The participant made gradual progress with her rehabilitation, thanks in part to her inpatient stay at a local rehabilitation facility. Her problems at the time of interview included fatigue, slow mental processing and right hemianopia. Despite this, she had started to read again, was participating in yoga with her husband and was using strategies to compensate for the right-sided inattention.

Helen had occasional headaches and some left-sided limb symptoms, although these were thought to be attributable to anxiety. The participants was still receiving support from a psychologist at the time of the interview. NIHSS score was 2 and EQ-5D VAS was 60.

9.7.5. Participant 5: Paul

Paul was a butcher in his 50s who lived with his wife. On the day of the stroke, the participant had finished his night shift and dropped his wife off at work. When the wife came home after her work, she found the participant collapsed of the floor and was unsure of how long he had been there. CT revealed a right-sided non-lobar ICH. The participant suffered from a dense left hemiparesis (including face) and dysphasia.

The participant had been married for nearly 30 years and had sons and a daughter. The participant admitted to drinking about 2 bottles of vodka per week but claimed he did not get drunk, did not experience withdrawal symptoms and did not need alcohol first thing in the morning.

The participant had a mismatch of expectation vs reality. He had expected to recover to his pre-ICH level of functioning and was frustrated with not being there yet. He was also deeply dissatisfied with the healthcare he had been provided as he had expected more rehabilitation and physiotherapy. The participant had recently started to be able to walk some distance independently with a quad stick. NIHSS score was 11 and EQ-5D VAS was 50.

9.7.6. Participant 6: Dawn

Dawn was a baker in her 40s who lived with her husband and son. She had a primary non-lobar ICH in the left side. MRI revealed multiple non-lobar microbleeds, white matter changes consistent with small vessel disease and a possible left sided lacunar ischaemic stroke. The participant also suffered from hypertension that had been difficult to control.

ICH caused weakness in the right arm and leg as well as sensory loss down the right-hand side. These deficits had been gradually improving. Weakness in the right arm had meant that it was not possible for her to return to work. Central post stroke pain had been a problem for which she was taking Gabapentin. She also described frequent headaches which were quite severe, generalised and were sometimes accompanied by nausea with occasional flashes in her vision, as well as the need to sit down and rest. She experienced these headaches at least three times per month.

On the week of the interview, the participant had suffered a right-sided bell's palsy with no obvious explanation. Although she has regained a considerable degree of mobility, she was unable to put fully dress herself, button her clothes or write. NIHSS score was 2 and EQ-5D VAS was 70.

10. Results: Qualitative interviews

It would be difficult to overstate the impact that the intracerebral haemorrhage had on the lives of those affected. Participants experienced major changes due to loss of work, financial difficulties, inability to drive, and the loss of friends, leisure activities and social activities. Most interviewees (participants and family members alike) readily identified profound ways in which their lives had been affected since the ICH. In the quotations below, some of these issues have been illustrated.

Analysis revealed four main themes relating to how survivor's and their family members experienced life after stroke. In the presentation of findings, the overall effects of the stroke on survivor's sense of self and identity will be described. Examples will then be given of the processes of adaption and adjustment that participants go through to minimise the effects of their functional limitations, including the use of health services and social networks to support this. Next, the findings move on to discuss the effects of uncertainty on participants quality of life, before finishing with some of the ways in which the stroke has impacted on family members. Each of the participants has been given a pseudonym that appears in brackets after the quote.

10.1. The effects of stroke on sense of self and identity

This theme illustrates the tremendous impact that a chronic disabling condition like intracerebral haemorrhage can have on a person's sense of self and identity. This theme has been explored through five sub-themes: 'no longer the person I used to be', 'changes in ability to perform simple everyday tasks', 'not being able to engage in usual activities', 'impact to working life' and 'impact of cognitive impairment', each of which will be discussed in detail below.

10.1.1. No longer the person I used to be

All respondents discussed how their lives had changed, often indicating how they could no longer be the person that they used to be before the stroke. This change was particularly devastating for some:

I've always been an independent person. I'll not ask anybody for anything. I've done it all myself... and to have to ask for help has been devastating. That's been the hardest bit of the stroke... having to adjust to getting help and not having the life that I had before. I worked my full-time job. I had a wee job at the weekend I used to do... I've had the three kids. I was always on the go, always doing stuff, and having that taken away from me has been really... sorry... has been really, hard to adjust to, because that's what I know. That's my life... I'm not the person that I was before. I was outgoing. I used to... go to the bingo or I used to do ballroom dancing, and things like that. That's been taken away from me because I can't do that now. (Dawn)

I keep saying it, but it's frustrating because you feel like you're a failure... that's how I feel because everything that I could do before I can't do as good or as well. And it's...it's a struggle... to come to terms with that. (Dawn)

In this first account, the respondent emphasises how the effects of the stroke were far reaching and affected all aspects of her life. Almost everything that the participant valued had been taken away: her independence, her capacity to work, her social activities, as well as her ability to look after her children. This last point had been particularly difficult for the participant to adjust to. Identification of roles was associated with a sense of self-identity; feelings of helplessness and frustration were frequently expressed in relation to forced changes in role. Having a stroke can have a profound impact on participant's ability to help others, and this change of status from giver to receiver was very deeply felt by some of the respondents. This was particularly stressful for Dawn, who was finding it hard to accept that she was no longer able to fulfil her role as wife and mother, particularly as an independent person in the past who had never relied on anybody to do anything:

My kids and my husband have always been there, but at the same time it's like... they've been there but they didn't understand fully what I was going through. They're trying to help, 'Mum, it's alright, we'll do it', but they didn't realise that was making me worse. That's what I should be doing and they're...taking it away from me. And it maybe sounds selfish but it's just...that's how it was, that...what they thought they were doing to help me was taking away even more of my independence... And wee things that I could scrape at doing: 'Just leave it, we'll do it'. And I thought...no I want to do it. I want to feel normal. I want to feel like I should. Like I'm your mum, ken. I'm your wife, ken. I don't want to seem like I'm any different, even though I am. (Dawn)

For one of the participants with young children, not being able to read to them or pick them up from school became a difficult reality. Although the participant recognised that they should be focussed on getting better, not being the person that they were before brought on intense feelings of guilt:

Guilty for my wife, thinking I could never be the husband she married ever again. Guilty for my kids thinking I could never be the parent I thought I could. Guilty as a friend thinking I could never be a friend the way I have been. Guilty in general. (Adam)

While physical impairments reduced opportunities for getting out, perceived personality changes were deeply felt by many of the participants. Some were uncomfortable with their current disabled state and were either ashamed or did not wish to burden their friends or relatives with their poststroke selves:

Everything's more of an effort.... so you kind of step back from what you were or what you done before... 'Cause you don't want to be a burden on anybody. I mean, we went away on holiday... and [it] was so hard 'cause I couldn't walk properly. So I felt embarrassed... like even going down to the beach or going down to the pool... I was walking like Quasimodo, this limp, dragging my leg... ken, I just didn't feel right and I felt insecure... (Dawn)

You go out for something to eat and people... if you're dropping your food or getting your cutlery the wrong way around... they automatically turn and look. And it's... to me it's embarrassing. And they're probably not giving it another thought, but some people you can see them whispering... it's hard. (Helen)

Some stroke survivors felt frustrated, especially in circumstances where they lacked control. Some of the participants described feeling as if everything, including their choices, had been taken away from them. For example, one of the participants struggled with having to ask others for help:

Your dignity, you've none! And as much as other people are trying to respect your wishes and that, it's hard saying, 'Right, can you take me to the toilet and clean me?' 'Can you dress me?' 'Can you help me out of my bed?' 'Can you help me down the stairs?' Ken, no being able to cook for your family. No being able to do anything for your family! The physical

side was hard but I've always said the mental side's been even harder.
(Dawn)

Some stroke survivors were able to cope with this change, while others experienced degrees of depression. Paul initially felt like *"life was not worth living"* as he thought he could *"never walk again"*. His attitude has now changed, and he remains hopeful that he will be *"able to stand and use my hand again"*. For one participant however, these feelings of depression were brought on from lack of understanding of others. Dawn struggled to convince others that she could no longer do things like she used to:

I was getting really depressed about it because outside, people think, 'Oh she looks fine'. But they didn't know the struggles I was going through... having to get people to cut up my food for me... no being able to hold a fork properly and having to use my other hand, and then sitting with a lap tray and a bib and things like that, ken. It was like... I felt like a kid. (Dawn)

10.1.2. Changes in ability to perform simple, everyday tasks

Almost every participant reported how having a stroke had radically changed their lives. Survivors noted changes in their ability to perform simple, everyday tasks such as getting washed and dressed, making a cup of tea, filling in letters etc:

I mean, it was so hard. Not being able to do anything. Couldn't dress myself. Couldn't put my bra on. Going to the toilet, I couldn't clean myself. I've had to teach myself to write with my other hand 'cause I couldn't hold a pen. I couldn't cook. I couldn't hold a knife, 'cause I've no feeling in two of my fingers. Cutting food is still a nightmare. I still struggle with things like that. Couldn't lift a cup out the cupboard or cutlery out the drawer. I just didn't have the grip. (Dawn)

Some reported how much more effort was required to do things which had seemed simple before:

Everything takes longer to do now. Ken, it's no just a case, 'oh give me that and I'll do it', ken. It's, 'right, oh here we go'. Kind of, got to psyche yourself up to do it... I used to have a couple of hours sleep and I'd be up and that'd be me all day and night. And now it's...everything: hoovering, dressing myself, making a bed. Everything is such an effort! Things like that can get you angry and frustrated, 'cause you feel stupid. You're no, but... you feel it. (Dawn)

The thing with Stroke as bad as mine is, you cannot do it yourself. That's what left me helpless. But after a few weeks, I felt that I could do the things that people were doing, even if I needed to struggle with it. (Adam)

I'm just a bit slow at doing things now, 'cause my hand's slower. (Jim)

These residual impairments and disabilities were a great source of distress, with one of the participants feeling like a failure because of them:

I keep saying it, but it's frustrating because you feel like you're a failure... that's how I feel because everything that I could do before I can't do as good or as well. And it's...it's a struggle... to come to terms with that. (Dawn)

10.1.3. Not being able to engage in usual activities

Loss of valued activities for participants included disruption to their employment, ability to drive, recreational activities and ability to socialise with friends. Many of the interviewees had rich and varied social lives before their strokes. Having the stroke often left them unable to engage in those activities that had been regular aspects of their lives previously. For example, physical impairments made previous recreational activities impossible for Dawn:

I'd maybe go to the bingo or I used to do ballroom dancing, and things like that. That's been taken away from me because I can't do that now. It's harder to do. 'Cause I've still not got the full power in my arm. Trying to hold a frame as they call it in the dancing, or carrying out the moves... it's tricky when you've no got full power in your leg and got a bit of a limp and your arm's no the same... (Dawn)

Two of the respondents used to be very physically active before their stroke, engaging in sports such as running, cycling and swimming, which they could no longer do. Even less physically vigorous pursuits were restricted after stroke, as most respondents reported that they could no longer engage in activities such as cooking, gardening or reading:

I can't read anymore. I used to be one of these people who always had a book under my arm. Instead I listen to the audiobooks, but it's not the same. (Helen)

When the residual disabilities following the stroke prevented the participant from engaging in activities that had previously been an important component of their identity, then their well-being tended to be considerably reduced:

The hardest thing is not being the person that I used to be. I used to be really active. I loved my job. Now I can't do any of that. (Helen).

Interviewer: How have things been since you've been back home?

Participant: It's been a struggle, and frustrating, to be honest... I like to be a hands-on person. I've always been somebody on the move. All the time. Somebody that would be up there, or be out there in the car... So, I think I've had to learn a lot of like, well... this is going to be sore for you, you're going to have to give into this, and so... well that's what I've done. Or else I wouldn't get on. And, it just annoys me. At times.

Participant's Wife: And it would get him down if he seen me out there in the garden, he would get all upset. He wanted to be outside doing it... what I was doing. And then he'd sit and apologise to me because he wasn't able to help me: 'I'm sorry hen, I'm sorry, I want to be doing that with you'... You know? (Paul)

None of the stroke survivors were able to drive at the time of interview. Participants who experienced a disability that prevented them from driving found it to be a significant handicap and an erosion of their independence:

Interviewer: So what's the biggest thing that you can no longer do that you could before?

Participant: Driving is one of them. Because I like going everywhere. I had two cars. Ehm... I just like driving. And I like going to places. Like I was saying to my wife the other day, I'm not the type of guy that come the weekend I'd go I'm away to the football with the guys. I was more like, 'come on, we'll go away down to Berwick'. That's how we led our lives at that time. And I miss that, you know. (Paul)

That's my main bugbear as a result of it is that I've not been able to drive... Until you can't drive, or told you can't drive, you have no idea how much you take driving for granted... It's the independence that goes. (Colin)

10.1.4. Impact to working life

Respondents expressed frustration at not being able to engage in their intellectual pursuits that had been an integral part of their prestroke identity. Five of the survivors could no longer engage in their work-related activities (the other was already retired prior to the stroke). Their residual impairments and disabilities were therefore a great source of distress, often leading to a reduced quality of life:

They've said that I'll never be how I was... before I had the stroke. I have to come to terms with that. That life... I'll never ever go back to work. I'll never be able to stand and do the job that I was doing... I'll never be like that again. I've got to let my body know that I'll not... I'll no be able to do things that I could do before. (Paul)

One of the participant's wives found it particularly distressing having to come to terms with their husband not being able to work. They had accepted that the participant would not be able to go back to his previous customer service role because of his aphasia:

He couldn't do it because he can't get his words... he gets frustrated. And sometimes we don't know what word's going to come out! (Jim's Wife)

However, his wife felt that despite what the occupational therapist had told them, there must be an environment that would be suitable:

Participant's wife: When I phoned [the occupational therapist] up, she says she didn't think it was worth her while... [because] in her opinion, he was never going to work again. Which, kind of upset me... To have somebody say that they never think your husband's going to work again...it's hard. And I couldn't understand that, because I thought, well we know his speech is not very good...but he can function. He can walk. Can lift things. So there must be a role somewhere. You can't just turn round and say, 'you'll never...' you know, he's only in his fifties! (Jim)

As many of the effects of stroke are invisible, some of the participants found that other people quickly forgot that they had a stroke and expected too much of them. Although one of the participants had accepted that she would no longer be able to work as a result of her residual impairments, because she 'looked fine', she felt pressure from those around her to return to work:

I was getting a bit of problem from my work. They were contacting me like, 'when are you coming back?' 'Cause obviously it's a wee village and people were like, 'oh we've seen her walk to the corner, so she must be fine' and er, because my face and that wasn't affected, people maybe just thought I had a sore leg or that. People didn't know... They just assumed that I was fine. So my work were giving me a lot of hassle... Wanting to know when I was going back... They didn't realise I couldn't hold cutlery. I couldn't go back and prepare food. I didn't have the power. Didn't have the means... It was getting quite frustrating. I was getting really depressed about it... (Dawn)

10.1.5. Impact of cognitive impairments

Many of the participants alluded to long-term cognitive impairments. While some participants described losing concentration whilst reading a book or forgetting to take medication as changes from pre to post illness, for others, the change was much more marked. One participant described how she used to have a '*really, really sharp memory*', and that it had been a running joke among the family that she would '*forget nothing*' and '*ken everything*'. Since the stroke, the participant has struggled with her short-term memory and feels as if it's continually getting worse:

Over the last few months, I've noticed my memory's a bit... less than what it was. Like, forgetting dates... appointments... things that I had on. Whereas before I was like: 'I'm doing this', 'I'm going here', 'The weans have got this', 'They're doing that', and I could rhyme them off, ken...it's frustrating now, 'cause the wee boy's transitioning up to the high school, so they've got a lot of dates coming up of what they're doing and where they're going and things like that. And it's a nightmare, cause he'll say, 'Mum, where's that letter that I had to...'? And I'm like, [sharp intake of breath] what one was that?... Whereas before I'd say, 'oh right, that's filled out and it's sitting there'... And I just, kind of, feel useless... I just want to be normal. (Dawn)

The participant then goes on to describe several instances of doing things that were out of character from how she had been before the stroke:

I mean, the other day there my husband went in to the fridge and there was the iron lying in the fridge. I'd done ironing... And then when it was cool, I went to put it away and I put it in the fridge...and I knew it had to go in the cupboard

but I put it in the fridge... And all that... That's nothing. It's nothing. But it's like... the other morning, the wee boy had a letter and he showed me it and I filled it out and he never took it to school. I lost it. In the space of five minutes, I lost it. And it was in the oven. I put it in the oven! Why I put it in the oven, I don't know. And I tore my cupboard... my wee drawer apart that I keep all the letters and things. It wasn't in there. I checked his school bag. I checked his packed lunch bag. I checked the... I even checked the fridge. Checked everywhere. And then it was that night, we had to put the oven on, and there it was. It was in the oven. So, I mean, things like that... ken, it's out of character. And it's... the other day there I run my kid's bath. And I said, 'mind and check it before you step in to it'. And he's screaming... It was freezing cold water. I'd run the bath with cold water. I always put the hot in and then top it up with the cold. I'd done it the other way round and it's like... things like that that are more frequent... (Dawn)

For one of the participants, problems with speech was the biggest thing to happen to them. Adam 'couldn't face not being able speak properly ever again'. Speech was everything to this participant. It was the difference between being able to communicate with his wife, kids, and friends. In addition, because of the nature of Adam's job, he faced significant difficulties when trying to get back into work:

I have only been looking for one month and had four interviews, so things are progressing well. It's just different and, somewhat, surreal. I used to be okay at interviews, never been out of work since I turned 17 but things have changed. Now I cannot explain things, like 'tell me about the time that you turned things round from a customer experience perspective'. I could if it was writing the answer, but speaking is a different beast. (Adam)

Other participants described difficulties they faced when trying to remember people's names or describing things:

It's funny. Sometimes you just can't... you can't talk. I really don't know what it is... you'd like to talk to people... but you can't because you forget who they are... And it's awful saying, 'I don't know who you are'. And then other times I can... ken, I don't know, it's...it's strange... Sometimes it works and sometimes it doesn't. I don't...I really don't know. I mean, compared to what I used to be, it's bad. You know, before I had this stroke. It's really quite...I could do things no problem... Now, I don't know who they are. But I know who they are. It's really stupid. But what can you do? Somebody talks to you, you try to talk to them but...It's just one of these things. I...I don't know. The people that know

you are okay, but the people who don't know... people are a bit strange. It's just the way it is. (Jim)

Trying to describe stuff was a nightmare! I could see what I was talking about, but I couldn't get out the words of what I was trying to describe and...um, well I would get frustrated, 'cause I could see it and I'm trying to describe...and I'm going round this big circle trying to describe one simple wee word...so that was...it was really frustrating. (Dawn)

As mentioned previously, Colin's biggest concern was undergoing a driving assessment so he could regain his licence. Although he felt as if he had not been affected by the stroke, at the driving assessment, he was found to have a cognitive assessment score indicative of cognitive impairment. According to the notes from his driving assessment, Colin had difficulties in maintaining a safe road position and would adopt quite a wide position to the right without being aware of this. He also had difficulties anticipating the road traffic environment he was approaching, which led to several errors in judgement and decision making. His reactions and decision making were quite slow at times, as was his speed of travel, particularly when he was distracted by navigating more complex road traffic situations. There was also one significant lapse in concentration at a pedestrian crossing. On approach to the crossing he had failed to notice that the traffic light had changed to red and failed to slow down as a result. It was therefore decided that his medical condition was having an adverse impact on his ability to drive safely. Despite this, the participant seemed unaware (and unaccepting) of the impact that the stroke was having on his judgement and speed of information processing:

Interviewer- Do you know why they failed you?

Participant- Yeah, they came up with some stupid things about my driving... like, when I got back to the hospital... this is a daft one this.... Ehm, I can't remember now exactly what happened but they marked me down because I moved out and there was a van coming. And eh, they said that, you know, it was dangerous. But, again, I keep on saying to them that it could of happened to anybody... It's nothing to do with the stroke... I didn't move in front of that car because of the stroke. It was just bad driving on my part... And nothing to do whatsoever with the stroke. (Colin)

10.1.6. Summary

Following the stroke, all individuals felt that some aspect of their self had been disrupted. Common challenges included a compromised ability to perform activities of daily living, in addition to problems with speaking and remembering. These challenges often improved over time however, the lasting impact tended to manifest as a feeling that they were no longer the person that they used to be. Individuals perceived themselves differently due to changes in their ability to fulfil certain roles (e.g. in the family or workplace), and their ability to engage in activities that were important to them, including driving and having active social lives.

10.2. Adaptions and adjustment

The theme 'adaptions and adjustments' illustrates the different strategies that participants used to minimise the effects of their functional limitations. This theme will be explored through three sub-themes: 'ways of adapting to disability', 'benefits of health services' and 'help of social supports'.

10.2.1. Ways of adapting to disability

Although participants were willing to accept that their capabilities had changed, they were determined to reclaim activities that were important to their sense of identities. For one of the participants, being a DJ was an important part of his social life. After the stroke, he had worried that he would never be able to DJ again due to his right-sided weakness. Determined to get this activity back, and with the encouragement of his wife, the participant started to practice with his left hand at home. Although a bit slower, the participant was pleased to inform me during the interview that he was now able to fully engage in this activity and had played a slot at a local soul festival the month prior. According to his wife *'he got a good reception'*.

Helen, who had been physically active prior to her stroke, spoke about her difficulties when being in crowded places. Her right hemianopia meant that people often seemed to appear out of nowhere, sending her off balance. She had recently started going for walks by the canal as it was a safe environment, where she felt comfortable going out of the house by herself:

The paths are really wide which makes it easier. You're not getting in people's way, or going to bang into something. Whenever I walk there I feel normal. Like how it was before the stroke. (Helen)

Engaging in adaption to disability was important for survivor's quality of life, even for more simple day-to-day activities. From using an app that would read recipes aloud, to re-arranging clothes in drawers to make everything easier to find, participants gave several examples of ways in which they had adapted their homes to make life easier:

Everything in my kitchen used to be black, which made it difficult to see. So we decided to buy everything in red. The kettle, toaster.... It makes them easier to find. We also re-arranged the jars so that they're always in alphabetical order-coffee, sugar, tea. (Helen)

Individuals who had started to adapt to their disabilities often made optimistic statements about their situation and made more positive social comparisons to indicate how fortunate they felt they were. For example, even though Paul was still not able to walk without an aid, he felt grateful that his speech hadn't been affected and that he could think for himself. Likewise, although Colin couldn't drive as a result of the stroke, he felt grateful that the stroke was not worse than it had been and felt lucky in comparison to others:

I've been very, very lucky with my stroke, because a lot of people with strokes find that their arms are like that... or they can't walk... Or they can't talk properly or whatever... So I've found that I've been very very lucky. Very lucky indeed. (Colin)

10.2.2. Benefits of health services and resources

It was evident that various resources were important for participant's ability to successfully engage in adaption and report a positive sense of well-being. All survivors identified the help they received from rehabilitation programmes as extremely important for enabling them to overcome their disabilities and to learn new skills:

Participant's wife: Well he does... you do woodwork there [speaking about the local stroke club]... They've made quite a few things with his hands...um, a lot of things for the garden...The twirly thing...and the plant...there's two planters now. Er, and he's done one each for his daughters... the girls, and he's doing

one for his mum... So that's something that he's never done before. So that was really...we think that's really good that he's done that. (Jim's Wife)

Rehabilitation goals were initially centred around the ability to perform simple, everyday tasks, for example, to be able to 'tie shoelaces on trainers', 'make a cup of tea' and 'string more words together'. However, participants also set goals that would allow them to re-engage with those activities that had been an integral part of their poststroke lives. For instance, the occupational therapist set goals with Adam that revolved around his children, for example, being able to take them to bed and bathe them. Similarly, Helen specifically identified the help she received from the psychologist, where a home visit every couple of weeks helped her to come up with strategies to use the bus by herself and attend family events without feeling like a burden:

I've only just finished seeing the psychologist. She would work with me and I could tell her things that I was finding difficult. Like my niece's wedding. I didn't want to go. I get really tired and I was worried that I would use my cutlery the wrong way or drop my food. But we talked about it and she came up with suggestions, like booking a room at the hotel so that I could go for a nap. And having my family... like my husband beside me, in case I got the knife the wrong way round... I ended up going, and it was great! (Helen)

In addition to helping with rehabilitation goals, many of the participants spoke about the emotional support that they received from healthcare practitioners in the community:

Participant's wife: Your speech therapist was superb and they very quickly built up quite a good bond and she was really good, a very good emotional support to [participant]. And to me... she was really, really good and a very good...I felt it was more than just speech therapy she offered. In the sense that she'd built up a really good rapport with [participant] and she sensed if he wasn't doing so well that day in terms of confidence... And she would spend time talking with him about it...

Participant: But, er, also... my physio, I mean, she was brilliant mentally as well...as physically. She was amazing. Wasn't just the physio side she was there for. I mean, she was there for the mental side, for the days that I was having my breakdowns [laugh] and things like that... just feeling sorry for myself and...and she...she was really good for that. (Adam)

Stroke survivors who were discharged into the care of rehabilitation services in the community often spoke positively about their experiences and commended staff involved in their on-going care. However, they also spoke about the inconsistency in follow-up and the rehabilitation process post-discharge from hospital. For example, it took several weeks before services were put in place for Paul. He stated feeling like he could have been '*doing a lot more*' and should have been '*wasting less time lying around*'. Similarly, Jim never received physiotherapy in the community, causing a great deal of distress for him and his wife as they believed that the lack of adequate access to therapy hampered his recovery.

This lack of structured rehabilitation for stroke survivors led to some feeling isolated in the community and being unaware of support services:

The downside about being back home... It's like the hospital just forget you... and once you are discharged you are on your own. (Adam)

Wheelchair transportation and other mobility aids were named as an important resource, helping survivors with mobility disabilities to get around and return to valued activities. Paul was initially reluctant to get a scooter, as he wanted to be able to walk again. However, his wife eventually convinced him, stating that it was just a temporary measure until he got better and that it would help him to do the things that he wanted to:

So when I sat and thought about it, I thought, wait a minute, I could go walk with my wife, and I could go down to the shop with her at the same time... And went, aye that's what I'll do! So I've got the scooter. If the weather wasn't like this I'd be out in it today... I've been on a wee trip with the wife up North. I can get on a bus with steps. Get in the chair thing. So... the last few months I've been really good, because of that... Things are getting better... The quality of how I can get about, is totally changed from when I first came home. (Paul)

10.2.3. Help of social supports

Despite the changes in social relationships and family roles as noted in the sections above, survivors indicated that they benefited from the help of various social supports- spouses, family members, friends- as providing emotional and instrumental supports that were important in their poststroke lives. Helen identified her husband as a key source of support and gave examples of the ways in which he was helping her adapt and adjust to life after the

ICH. In addition to joining yoga together to help improve the participant's balance and raising the beds in their allotment so she could start gardening again, Helen's husband was also helping her to read to her grandchildren:

My husband will read the book with me first and then I memorise it so I can read it to my granddaughter. I don't want her to think her grandma can't read.
(Helen)

Similarly, Adam's wife, who used to be a primary school teacher, would download resources and do extra speech and language therapy with the participant. Without a spouse, one of the stroke survivors relied on other family members for social support. The participant had recently been widowed and identified his sister as the one providing support with activities such as driving and shopping:

Anywhere I want to go, my sister has to take me. Luckily she only works in the evenings so therefore if I ever want to go somewhere in the day, like to the shops, she can take me... (Colin)

Stroke survivors also benefited from the support of peers. These supports were not only important for the provision of emotional support, but also for well-being, as they helped the survivors to maintain important aspects of their prestroke identity:

Participant's wife: And he's got...I mean, he's got good mates, and, umm...

Interviewer: Did you find that your relationship with friends changed at all?

Participant: No, I...I thought that, err, they generally got, err, closer as well. You know? Because, err, I...I saw some of them once a week in the hospital. Err, and I'd never seen them that much before [laughs]...You know what I mean?

Participant's wife: I...I think, yeah, I think it...it hit a chord with a lot of his pals...And it made them realise, you know, how, like, quickly life can change...
(Jim)

Attempts at adaption can fail if social support is negative. Absence or withdrawal of support can have an ill-effect on survivor's well-being:

Interviewer: Has the stroke changed your relationship with your family or friends?

Participant: [Sigh]. My friends, aye because [sigh] I feel they look at me different. Like...to me, I feel an embarrassment to them... And I know I'm no, and they tell me I'm no, but that's how I perceive it. I perceive that I'm alone in this...and you, kind of, single yourself out and, kind of, shy away from everything. Ken, so it has changed...ken, I was quite bubbly, outgoing, ken, ta-da, I'm here so to speak, ken. Life and soul and...and now I feel very self-conscious and I...I mean, I never cared what anybody said. I...I just...so what, ken. That...I am what I am and that's me. But it's made me more withdrawn... (Dawn)

Because I'm speaking to you like I am, as if there's nothing wrong with me, they don't realise how hard it is for me... That's the side they don't see. And I never show... I never show being upset or angry or anything. I just stay the same. But for me, there's times when some of them could say, 'awk well, I'm going up to the centre, do you want me to get you something, or take you?' They just assume that I'm not wanting to do anything like that. (Paul)

Similarly, not all spousal support is positive in the lives of stroke survivors. Dawn reported that she felt dissatisfied with the emotional support she received from family members. She admits to feeling lonely and wishes there was group for stroke survivors that she could go to for emotional support:

There was nothing here for me like that when I had the stroke. Like, other people so you don't feel that you're alone. Just to have somebody else say to me, 'oh I felt like that today' or 'I picked up my toothbrush and put my toothpaste on myself today'... I ken it feels good, but to other people, they'll just look at you and think, aye, alright, ken... But it's...to have they kind of things taken away from you and not have anybody to talk to about it... So for that side, it would be better if there was something in place... like even a support group. So you...don't feel like you're alone. 'Cause you do, you feel like... you're going through it and nobody else has. And that's...that's hard (Dawn).

10.2.4. Summary

Several respondents engaged in processes of adaption and adjustment following their stroke to minimise the effects of their functional limitations. All participants wanted to re-engage with familiar routines and activities, and to reclaim previously valued identities. For many, processes of adaption and adjustment required the use and support of health services and social networks.

10.3. Uncertainty

All respondents reported feelings of uncertainty throughout the course of their stroke. These feelings occurred at all stages of the stroke journey and were felt by stroke survivors and family members alike. This theme will be explored through the following sub-themes: 'uncertainty during stroke onset', 'uncertainty over course of stroke' and 'uncertainty about long-term recovery'.

10.3.1. Uncertainty during stroke onset

Stroke is a traumatic event. For many it is unexpected, and hits without warning; for others, the onset of stroke is gradual, with vague symptoms being experienced over the course of several days. No matter how the stroke started, while recounting the events leading up to hospital admission all respondents expressed uncertainty as they tried to understand exactly what happened. For many, the first signs of stroke was often a realisation that something was not quite right:

Participant: I came in from my work... I'd had a pounding sore head for about three weeks before it. And I felt like something was going to pop. It felt funny this time. Just felt like something was going to pop. That was the only way I could describe, like, when you see a balloon going to go and it's like...that this feeling I had...and I came in from my work and I just...I just felt funny. I went to sit down and I fell on the floor. And I went to get up and my arm was dead... and I had this metallic taste in my mouth... And then the...it started...my arm started tingling and it started...and I'm saying... it's no a stroke...but at the back of my mind somewhere I knew it... was some...something wasn't right. Er, so I sat on the couch and I must have sat for about ten minutes and I just had this horrible, horrible taste, a metallic taste in my mouth. And I went to move my arm and it was a dead weight. Couldn't move. And I went to stand up and my leg was heavy. And I'm trying to walk and I was dragging it. Every time I tried to move my arm, I just couldn't. Couldn't move anything at all down my right side. (Dawn)

For others, there had been no warning signs. This was particularly the case for Adam, who was at his peak fitness, and was competing in a marathon at the time of the stroke:

Participant: Err, about ten kilometres in, I took a...a sore head, and I...my balance really went off. Umm, and... I collapsed. My right side, err, collapsed, and I...I...I was speaking to the steward, err, and it was gobbledegook...that was coming out. Umm, so he said that he would phone an...an ambulance. Err,

so the ambulance came about five minutes, err, and then, err, I was bundled in the back, err, and then, err, err, I was taken to the hospital, err, where I was, umm, I was, umm, was...what was I? Err...

Interviewer: Assessed?

Participant: Yeah, and... Umm, then it was really blank because, err, I was obviously on morphine or something. Err, and then I was really away with it for three days... (Adam).

The onset of the stroke was vividly imprinted in the memory of stroke survivors as a sudden incident for which they were not prepared, and which changed their lives irrevocably. The sudden and unscheduled event seemed less problematic for some, while for others, it was particularly devastating. One participant described this experience:

But that day in particular, ehm.... I was exhausted the whole week. I hadn't been sleeping, at all! I felt totally exhausted. At work, just, that last shift I felt drained. Totally. So I was sitting here, watching the tele, and.... I felt... that something was wrong. But I couldn't... no sore or anything like that. No pain, nothing. I just put it down to tiredness. And.... Stuff like that. So, I don't know, maybe another hour had passed... so I remember, I got up, went to the kitchen, and I came back, and I sat down, and I went, I said no, something is wrong. and I couldn't put my finger on it. The next minute I remember, I turned round, and I watched my arm fall down. My left arm fall down. I watched it! So I went like that, aw nah.... Something's happening. So, I was trying to think, what am I going to do, I was starting to panic. So, I tried to stand up, and eh, get to the table there. Then my leg went as well. Then I fell. Then I remember, I was holding on. I was underneath the table. And I was holding myself up. And, ehm, I just kept on talking. And then I must have passed out. (Paul)

Across interviews, most participants could remember the onset of the stroke, however few could recall the first few days in hospital:

That was it. So...so that was the last time...um, and I don't remember anything, being in hospital or anything...Little bits and pieces, nothing for me, I don't know. (Jim)

Interviewer: When did your memories start kicking back in?

Participant: Uh... probably the day after. Over two days after...

Participant's sister: No, you were out for it for a week

Participant: Was I?

Participant's sister: You were in intensive care for a week. So it was about a week... I would say, It was about 7 days later... (Colin)

Many of the individuals were shocked that they had a stroke at such a young age, particularly if they perceived themselves to be in relatively good health beforehand. One of the participants struggled to accept that they had a stroke, believing that it is a disorder that only affects the elderly:

Participant: The thing is I didn't see it as...as a stroke. Err, I saw it as a brain haemorrhage, which...which is different from a stroke, you know?

Participant's wife: You...your perception...you still...you kind of have...

Participant: I...I still, aye...

Participant's wife: ...a stigma about a stroke...

Participant: Yeah.

Participant's wife: ...where you think it's an old man's thing. (Adam)

10.3.2. Uncertainty over course of stroke

Uncertainty was also difficult for survivors throughout the course of their stroke as they anticipated the likely degree of disability. For some, this uncertainty began in the first few days of being in hospital:

It felt as if you were a patient rather than somebody... who can get better. I was put in a ward... beside 3 other patients, who em... didn't even have similar conditions to me. I felt all alone... To top it off this was the time realised what position I was in... From, em, needing a hoist to get out bed... to needing a wheelchair to go to the toilet... (Adam)

Participant: I couldn't understand why they were keeping me here when I can talk alright and stuff like that. And then getting the physio, I was just getting upset all the time, crying all the time.

Interviewer: What was making you upset?

Participant: Em, you know... I could walk before, why can't I do it now? I couldn't realise the... I couldn't believe that.... How can I not... drive my car, or walk away or, stuff like that. And I'd be sitting on the chair in the hospital,

ehm... next to my bed... and I was just like, why is this getting done to me?
(Paul)

Many of the participants also felt a sense of uncertainty and unpredictability around stroke outcomes. Adam had a conversation with one of the healthcare professionals whilst in hospital that highlighted the unpredictability of recovery. Although the healthcare professional was simply highlighting the worse-case scenario, and reassured the participant that they would do everything to make sure this didn't happen, he found it hard to accept:

I didn't know what to expect but was unprepared for her chat... She basically said em, I might never walk again... might never speak again... the right side might always be disabled... I was taken aback! How can a fit and healthy guy go to this in a few weeks? (Adam).

Some survivor's behaviour poststroke was very changeable, making daily life uncertain. Jim expressed frustration with the uncertainty of his ability to speak on a day-to-day basis. He experiences receptive and expressive aphasia that can some days be more severe than others. He is never sure when his speech will give him trouble or when it will be more fluent:

Interviewer: And have noticed change in your speech?

Participant: Yes.

Participant's wife: Um...not since he woke up from his sleep. I mean, his speech was bad...

Interviewer: Right.

Participant's wife: I think it's got a bit better...some days... some days it can be absolutely...and other days, it's just...like, you know, being back at the beginning...

Participant: I'm no sure... Sometimes it works and sometimes it doesn't. I don't...I really don't know. I'm...I mean, compared to what I used to be, it's bad. You know, before I had this stroke. (Jim)

There was also a degree of uncertainty over whether participants would ever be able to do certain activities again:

And then, up at the hospital as well... I'd been up there maybe, two and a half, three months... And my wife kept on saying to me, what if I bring your laptop up. And I was like naw! I was frightened, I would open it and it meant nothing

to me or I couldn't do anything... I think a lot of it was just shock. And frightened. That's the two things I think... I was very frightened I wouldn't get any better. (Paul)

Once home, there was often uncertainty about survivor's long-term disability and the unreliability of formal support. Uncertainty about when therapies would start and how arrangements were made left some individuals and family members feeling abandoned:

Participant's wife: And there wasn't...we didn't know when she [speech therapist] was coming back, and it was no fault of her and she again...she ended up coming back and apologising saying you should have been passed onto somebody, because you were then just left and it was a real crucial time where you were starting to get really anxious... thinking I'm not gonna make progress, that's not...my speech is terrible. (Adam's Wife)

Survivors were also afraid of having another stroke. The uncertainty about whether a stroke would happen again persists over time and is coupled with the fear that the next stroke might be worse. For one participant, the fear of having another stroke, or of symptoms worsening, was still present two years after onset:

Participant: I kept on expecting some kind of physical manifestation of my arm not being right or my leg, not being able to walk on it. But it never materialised. And I kept on thinking about things like, I thought, surely my brains going to go shortly. And you know, I won't be able to reply to this letter or go on the computer. But things were fine. Surprisingly. I kept on waiting for something to happen.

Interviewer: Has that fear gone away now?

Participant: No, I still let her [sister] know that I'm going for a walk and ehm... if I'm not back within the hour or so she'll know that something has happened.

Participant's sister: He's still got that fear of having that....

Participant: You never know, I mean, I might, I might have a... another stroke (Colin)

10.3.3. Uncertainty about long-term recovery

The standard often used by patients to measure recovery was their prestroke lives. Some of the participants admitted to having dissatisfaction with the progress of their recovery and where they wished to be:

Interviewer: How long did it take you get the movement back in your arm and leg?

Participant: My leg was a lot quicker. My leg was only about maybe three months. My arm, it wasn't...about six/seven months...and even now it's still no...

Interviewer: Not back to where it was?

Participant: No. No. Nowhere near...in fact I'd...I've been getting physio at the house and then they started me on a programme at the local sports centre...kind of, building up my...my muscle again...in my arm and just...and that stopped in September. And it was...it was okay. It wasn't a hundred per cent, but it was a lot better...and then it started...the weakness started coming back again (Dawn)

Their expectations often did not match up to the reality of their condition. This gap highlights one of the major difficulties of adjustment, the acceptance of continuing and relatively permanent disability. At the onset of stroke, patients may still be hoping for a complete recovery. After a year, the realisation that this might not occur was usually difficult to accept:

People say to me, 'it's only been a year'. But I feel like...it has only been a year, but at the same time, I should be better than what I am. And then other times I think, ken, I am alright for it just being a year, ken...so it just depends, I think, what you're doing and how...how you feel... (Dawn)

Many participants had unrealistic expectations of how fast they would recover. It was only over time that some participants realised the long-term nature of recovery:

One thing that struck me... where your brain is concerned... things take a lot longer to heal. I have had knee injuries... back injuries, but you do physio and in few weeks you are back to normal. With brain injury... things take so much longer. Even when things have improved... it takes one bad day to put it back... and you have to start again. (Adam)

10.3.4. Summary

Although expressions of uncertainty varied over time, it remained a central reoccurring theme and related to both short- and long-term issues. Initially it centred on prognosis, likely degree of disability and difficulty in imagining what it would be like away from hospital. Once home, continued uncertainty about survivor's longer-term disability and the unreliability of formal support was evident.

10.4. Impact on family members

The theme 'impact on family members' revealed the ways in which the stroke affected the lives of three of the participant's spouses. Findings for this theme start at onset and continue through to one to two years after the stroke.

10.4.1. Hospital admission: uncertainty about prognosis

The few days and weeks after a stroke were often quite stressful for families as they had to deal with the shock of the event. Due to the sudden nature of the stroke, family members experienced anxiety about the prognosis and uncertainty about what the future would hold. Family members described themselves as agitated and stressed by A&E, particularly regarding lack of information. As one family member said:

Participant's Wife: As soon as we got to the hospital, I was taken away to the family room. But nobody gave me any information. I sat in the family room with [laugh] my daughter for about...nearly forty-five minutes...

I: Okay... And nobody told you what was going on?

Participant's Wife: No. They just said sit there...er, they...says, you know, they were taking him for a scan... But they didn't actually explain what was happening... (Jim's Wife)

IF the stroke survivor was found to have aphasia, this was particularly distressing for the family members. In addition to the inherent communication difficulties, aphasia was a new and scary experience for some of the survivors. As a result of these communication difficulties, it is important that any relevant information regarding the care of the patient is

passed on to family members. However, medical and nursing staff weren't always as forthcoming with information-giving as hoped:

Participant's Wife: You know, there's a time...time that he was really quite bad in there [referring to the hospital]. Um, on the night that I didn't... 'cause I had a special doo that night, um... it was the only night I was never at the hospital. And they moved him from a side ward in to a mainstream ward. He didn't know what was happening... and although he was still sleeping, he was still, sort of... He knew something was different...and, er, you know, strange sort of people round about him... Going in to a ward with five other people from being in a single room... you know... there was a lot of different activities going on... and his mood went down a bit and I had says [to the doctor], 'his mood's dropped a bit'... I'm, kind of, worried about it. 'Oh that's fine, so we'll put him on mood tablets'... 'because we expect this to happen'. But nobody explained that's what they expected to happen. Was his mood down because he went in to a different environment? I wasn't there! (Jim's Wife)

One of the aphasic stroke survivor's wives also vividly remembered worrying that the connection between her and her husband had been lost:

Participant's Wife: ...and although he knew who I was, there was still a...it was a very strange thing, like he...he knew that I was his wife, but it was almost like that connection between us had gone from his perspective, so the...like I knew that if he was really aware of everything, he would have been worried about me... and he would have been trying to go, it's okay, everything's fine... kind of thing, I'll be okay. But there was none of that and it was almost this slight kind of detachedness... It's really hard to explain and that's what I've... I was most worried about was what if he doesn't remember the connection that we have. He knows I'm his wife, but somehow in this...through this, you know? So that's what kind of upset me the most. (Adam's Wife)

Once patients had been admitted, family members had to cope with their symptoms, including physical limitations, cognitive impairments and the possibility of a second stroke. Expectation of recovery varied, with some of the family members fearing the worst:

Participant's Wife: I got a call to say, err, we've done the scan and it looks like he's got a massive abscess in his brain that's gonna need to be, err, drained and surgery, but he's not gonna be stable enough for that to happen just now. So it just felt like my world...that was the worst day for me...

Participant: That was two weeks after the stroke?

Participant's Wife: This was two weeks after... So that was the day I thought he was going to die because... they basically..., err, said that within a month, you can die or you can be, err... And I thought this is it, he's not gonna make it, it was, umm, horrendous! (Adam's Wife)

10.4.2. After discharge: adjusting to life at home

For many, returning home is a transition that is eagerly anticipated and one that signals a return to 'normal'. Often however, the reality is very different. One of the couples reported worrying about the practical implications and their ability to cope. With this couple, circumstances were also a bit different because they had a very young family, so they had to be sure that the wife was ready for him to come home:

Participant's Wife: We had one episode where staff were starting to tell Adam about him getting home and it was quite early, and he was getting all excited and I'm thinking, oh my god, you can't go home just now...because I can't cope with you at home, and the house isn't equipped for you being home just now... 'cause you were still heavily using your wheelchair and everything then and our bedroom's upstairs, and I'm starting to panic... and that's when it's really hard because you're like... I don't want to appear to you that I don't want you home... But at the same time, I've got, I mean, my youngest is only a year and a half! (Adam's Wife).

The transition from hospital to home was often an anxious time for families. A few of the participants spoke about the 'bubble' of being in hospital where your food, personal care and rehabilitation is all taken care of for you. Once home, a lot of this responsibility is taken on by the family member. There was also a sense of uncertainty and unpredictability over stroke outcomes. In the presence of consistent cognitive impairment, a few of the family members had to assume responsibility for every aspect of their mutual lives. For some, constant physical attention was also required for toileting or eating, particularly if the person had poor awareness of his or her limitations. Family members were therefore often unwilling to leave survivors alone in the house. One of the family members found the stroke survivor very dependent on them for all activities, something for which they had not been prepared:

Participant's Wife: I don't think there's enough information given...for me. You know, in hospital you're in this bubble...Because the staff are doing everything. And you know... if you ask a question, they will answer it, but there was never...you know, not a lot of information's given to you. But you see, you, kind

of, just go with the flow...and then you come to this point where they suddenly say, by the way he's going home on Tuesday. And you're thinking...panic sets in...you know. And then, you know, he came home and it was strange 'cause, I mean, nearly three months he was in hospital...and I thought, you know, I'm left to, sort of, cope with this and I don't know if I'm doing it right, am I doing it wrong, are we doing too much... doing too little?

Interviewer: And was there never anybody that you felt you could talk about that with?

Participant's Wife: No. Nobody at all. And you're suddenly left...you know, at night time. And you just don't sleep because you're thinking, if he gets up through the night, am I going to hear him? Is he going to fall? Is he going to manage, you know? So panic set in for me. A lot of nights lying crying, thinking, am I doing it right? (Jim's Wife)

Family members of stroke survivors required support in their roles yet this was not always available. Primary care could play an important role in the care of stroke survivors and their caregivers however, the feeling of abandonment that people with stroke seemed to experience following hospital discharge suggests this role is not being completely fulfilled. Lack of proactive follow-up from the hospital or primary care services left patients and family members feeling dissatisfied and unsupported. One of the family members felt that their husband had been forgotten and written-off:

Participant's Wife: We were told that he was coming out the hospital, um...and I...I did express to the hospital I was anxious about it. Um, and they're, 'oh no, we'll put this care plan...' and all the rest of it and I got the assurance and just before he came out of hospital, well there's been a delay because, you know...but community rehabilitation will be put in place. And don't forget you'll see your consultant six to eight weeks after you come out of hospital...

Interviewer: So what happened?

Participant's Wife: Well after a while we thought, we haven't had anything from the hospital. So we asked his GP to get in touch to find out. And I wasn't happy with the answer that we got back... 'well there's not a lot we can do for his stroke. So really we had better not put him through the trauma to come down and see a specialist, 'cause... we can't do anything for him' And that's it. So we've not had any contact since... (Jim's Wife)

Health professionals assumed that family members would provide most of the care needed, with little or no support. Preparation for caregiving seemed to be a neglected dimension

where spouses felt they could have benefited greatly from advice before their family member returned home. Information provided by professionals was often considered inadequate and was an unmet need. Information about stroke-related impairments, how to prevent future strokes, access to community services and benefits to which they might be entitled seemed to be particularly lacking. For some, a lack of information was an unnecessary source of anxiety:

Participant's Wife: What I would say was lacking for me from support was... that kind of support for families when something like this happens. In terms of just to get your head around, like, what to expect, what not to expect...and the kind of, umm, you know I was really worried in the early days when he got home of leaving him. I didn't want to leave him in the house by himself, I just...kept...I had this picture in my head of coming back and finding him lying on the floor somewhere... Then I became unwell, but it was all anxiety, really, but I think that's the thing I would say...that needs to be improved...is that kind of support. And I think because you hear about it with people who've got cancer, whose recovery can be just as long and just as hard, and there's great teams like the Macmillan nurses and stuff who give a lot of emotional support, financial support, you know, financial advice, etc...There's a whole package.... But there doesn't seem to be that in this case. (Adam's Wife)

Initially uncertainty at home was centred around the possibility of survivor's having another stroke or falling and was often given as a reason for not leaving survivor's alone. One of the participant's wives vividly recounts the worry they felt with regards to leaving their husband alone in the house and the difficulties this caused:

Participant's Wife: Um, when he was in hospital...you're in that bubble because somebody's looking after your husband and you can see the progress that he's making. But when you come home, you just realise... how hard it is...that you've got to be there constantly so you know... um, making sure he's safe, the environment is safe, having to think things through you know. Before when you used to say, 'oh I'm just going out to the shops', put your coat on and just go to the shops. Now I've got to think, can he come with me? If he can't come with me... is there somebody here safe with him? Or if I leave him, how long can I leave him for before I get back because he can't do a lot of things for himself. Uhm... He can make... a cup of tea...and he's now learned to make a sandwich, but that's...taken up to now.....to do that. So to be out the house for any length of time, he could be sitting without a drink or anything to eat and that's something you've got to think about... (Jim's Wife)

Even though some of the family members knew they could go out without the survivor, they felt it was unfair to go out and enjoy themselves. For example, a wife of one of the survivors talked about the dilemma that she faced during the summer holidays when taking the kids for a day out at the beach:

Participant's Wife: I was basically saying to the kids this is not gonna stop us being a family and doing family things, so that they don't see everything as a negative. And...or saying, well, we can't go there, 'cause Dad can't do that and I didn't want to make him feel that everything's having to change... But that was challenging as well 'cause the youngest one was in a buggy, and I had my husband in the wheelchair... but we had, I think, one family day out... down to the beach. We had a nice day and the kids wanted to go on the beach, but we couldn't take the wheelchair onto the sand, so he said, yeah, I'll just stay up here, and he found that really hard, because...he sat and...and that's where I felt completely torn because I thought, I don't want this, I don't want you sitting up there watching them like some old man. But at the same time the kids want to play on the beach, and I don't want to say, no, you can't go to the beach, it's a lovely hot day, so that was really, really hard... (Adam's Wife)

10.4.3. Summary

The three spouses of stroke survivors who participated in the interviews all spoke about the impact that the stroke had on both their lives. The sudden and unexpected nature of a stroke means that there is very little time for family members to prepare for a caring role, with family members often feeling like they had no support.

10.5. Chapter summary

Thematic analysis of the qualitative interviews identified four overarching themes relating to how survivor's and their family members experienced life after stroke: 'the effect of stroke on sense of self and identity', 'adaptions and adjustment', 'uncertainty', and 'impact on family members'. These findings indicate the profound impact that stroke due to haemorrhage can have on the lives of survivors and their family. Their lives of survivors are abruptly altered, with participants often indicating that they could no longer be the person that they used to be. In addition to finding themselves unable to perform simple, everyday

tasks, physical and cognitive impairments often prevented the participants from engaging in those activities that had played integral parts in their prestroke lives. Overall, the qualitative accounts suggest the necessity for individualised assessment of needs and a person-centred approach to the planning and delivery of services to best assist stroke survivors in coming to terms with their illness and its long-term consequences.

11. Discussion

This chapter will go through each of the principal findings of the study individually, relating them to existing literature, and discussing any differences. Next, the chapter will move towards a discussion of any clinical implications of the research, what questions remain unanswered and what further research is required. The chapter will then end by bringing the main findings together, into a succinct conclusion.

11.1. Summary of principal findings

11.1.1. Prevalence of pre-existing cognitive impairment and dementia

Using data from LATCH COG, I found that approximately 1 in 4 patients (23%) had cognitive decline prior to their ICH. Forty-one patients (10%) had cognitive impairment with no dementia and fifty-two patients met the criteria for pre-existing dementia (13%). The prevalence of pre-existing dementia was 19% in the lobar group and 7% in the non-lobar ICH group.

The prevalence of pre-existing cognitive impairment and dementia is similar to the findings of Cordonnier et al (2010) who recruited 417 consecutive patients with ICH. The prevalence of pre-existing cognitive impairment and dementia was 14% and 16% respectively. Although the proportion of patients with pre-existing cognitive decline in LATCH COG was slightly lower than that reported by Cordonnier et al (2010) (23% vs 29.5%; with this difference being present both with regards to pre-existing cognitive impairment and pre-existing dementia), this may be explained by the design of my study. Pre-existing cognitive decline was based on review of the patient's medical records, where diagnosis would have been made by a variety of physicians and methods (e.g. geriatrician, neurologist, psychiatrist, primary care physician etc). Given evidence of under-recording of dementia in primary care in the United Kingdom, it is therefore likely that I underestimated the prevalence of pre-existing cognitive decline (Iliffe et al, 2009). Despite this, other studies have demonstrated a similar prevalence of pre-existing cognitive decline to that of LATCH COG. For example, in a study of 166 patients with neuroimaging confirmed CAA, Banjeree et al (2018) found the prevalence of cognitive impairment before ICH (as determined using the IQCODE) to be 24.7%. However, the authors acknowledged that those included in the study were younger and had a lower IQCODE than

those who did not have an MRI and were therefore not included in the study. Collectively however, these data suggest that pre-existing cognitive decline is common in patients with ICH.

11.1.2. Factors associated with pre-existing cognitive impairment and dementia

One of the most interesting findings in univariate analysis was the association of CT neuroimaging markers of CAA (Edinburgh CAA criteria (CT only)) and SVD (composite SVD score) with pre-existing cognitive decline. The damage caused by the haematoma is clearly not the only mechanism contributing to cognitive decline and supports the hypothesis that cognitive impairment in ICH is also related to the underlying small vessel disruption. My findings add to the growing evidence that CAA and its resultant small vessel disease play an important role in the development of cognitive decline in patients with ICH (Banjeree et al, 2018).

While participants without pre-existing cognitive decline had a median modified Rankin score of 1, those with pre-existing cognitive impairment and pre-existing dementia had median modified Rankin scores of 2 and 3 respectively. The finding that pre-existing cognitive decline is associated with higher levels of disability is echoed in a study by Yim et al (2018) who recruited 3537 participants with ICH. Like LATCH COG, dementia prior to stroke was defined as a positive history in medical records or treatment with cognition enhancing medication. In addition to the finding that dementia was associated with greater levels of disability and less independence at 3 months poststroke, the authors also found that pre-existing dementia was more common in lobar ICH than non-lobar ICH.

In my study, logistic regression analysis showed that patients who had a lobar ICH were twice as likely to exhibit pre-existing cognitive decline and 3 times more likely to exhibit pre-existing dementia than those who had a non-lobar ICH. In the study by Cordonnier et al (2010), the prevalence of pre-existing dementia was 23% in patients with a lobar ICH, compared to 12% in patients with deep haemorrhages. Lobar haemorrhages are associated with cerebral amyloid angiopathy, which often occurs alongside an Alzheimer's disease pathology (Arvanitakis et al 2011). Available postmortem data from 5 patients with lobar haemorrhages in the study by Cordonnier et al (2010) confirmed both Alzheimer's disease and CAA pathology.

In line with these results, pathological results from another study demonstrated that in 109 ICH patients, Alzheimer's disease pathology was found in 68% of CAA-related ICH patients versus 9% of non-CAA-related ICH patients (Attems, Lauda and Jellinger 2008). It is therefore possible that the higher rates of pre-existing cognitive decline in lobar ICH patients could result from the underlying amyloid-based pathologies, including Alzheimer's disease and CAA, and the interplay between the two (Ghisso et al 2011).

Patients with central (deep) atrophy were over 4 times more likely to exhibit cognitive decline and 8 times more likely to exhibit dementia before their stroke than those without, suggesting a neurodegenerative process. Severity of white matter changes (SVD score) was also associated with pre-existing dementia. The finding that white matter damage is associated with pre-ICH cognitive decline was previously shown in the study by Viswanathan et al (2008), who found that MRI markers of chronic tissue disruption (as measured by the global mean apparent diffusion coefficient) was associated with pre-ICH cognitive impairment. Cordonner et al (2010) also found increasing severity of leukoariosis (white matter hyperintensities on MRI) to be associated with pre-existing dementia, but only in patients with deep ICH.

In line with previous findings, increasing age (Cordonnier et al 2010) and haemorrhage volume (Liale 2017) were also associated with an increased likelihood of patients having cognitive decline prior to their ICH.

11.1.3. Incidence of new-onset cognitive decline at 6 months

Cognitive impairment is frequent after ICH with 43% of LINCHPIN COG participants scoring <26 on the MOCA at 6 months. This is significantly higher than the general population. Recent clinical and population-based samples suggest a mild cognitive impairment prevalence of 10-20% for adults aged 65 years and over (median age of LINCHPIN COG was 72 years), although lack of standardised diagnostic criteria and differences in sample characteristics across studies have led to significant uncertainty around these estimates (Petersen 2011; Langa and Levine 2015).

In a study of 44 survivors of ICH, Tvieta et al (2014) found cognitive impairment to be a frequent finding after ICH, with 61% of patients scoring <24 on the MoCA and as much as

71% of patients scoring <26. Another study including 78 survivors of ICH reported cognitive impairment without dementia in 77% of patients (Garcia et al, 2013). In this study, cognitive impairment without dementia was diagnosed when participants showed a significant impairment in one cognitive domain (according to a comprehensive clinical and neuropsychological assessment) without significant impairment in activities of daily living. Although these studies found a higher frequency of cognitive impairment during follow-up than in LINCHPIN COG, data on pre-ICH cognition was not available, potentially leading to bias in the reported incidence.

More recently, a prospective study was conducted to determine the prognostic factors for cognitive decline in ICH patients (Benedictus et al, 2015). In this study, of the 167 consecutive ICH survivors without pre-existing dementia, 62 patients (37%) showed cognitive decline during follow-up. The slightly lower incidence of new-onset cognitive decline compared to LINCHPIN COG may be explained by the use of the MMSE. The MMSE is a rather crude measure of cognition and may lack sensitivity to vascular cognitive impairment, potentially leading to an underestimation of cognitive decline.

11.1.4. Incidence of new-onset cognitive impairment and dementia within 1-5 years

During the first 5 years of follow-up of LATCH COG, of the 168 patients who survived longer than 30-days after their ICH, 47 patients developed new-onset cognitive decline (cognitive impairment and dementia). Cumulative survival rates for patients remaining free of cognitive decline were 82% in the first year and reached 65% at 5 years. During the first 5 years of follow-up, 22 patients developed new-onset dementia. Cumulative survival rates for patients remaining free of dementia were 95% in the first year and reached 84% at 5 years. Dementia diagnosis were about two-fold compared with the general population where current estimates in the UK suggest that the total age-standardised prevalence of dementia for those over 65 years is 7.1% (Prince et al, 2014).

My findings extend those of a recent nationwide population-based cohort of stroke survivors where 10-year absolute risk of dementia (based on data collected in medical databases) after ICH was 8.89% and 30-year risk was 13.3% (Corraini et al 2017). Compared with the general population in Denmark (comparison cohort matched to stroke patients by age and sex), the

hazard ratio for dementia among ICH survivors was 2.70 (Corraini et al 2017). Haemorrhagic stroke survivors were found to have higher relative risks of dementia than ischaemic stroke survivors- unadjusted hazard ratios were 1.72 after ischaemic stroke and 2.70 after ICH. In this study, ICH survivors were younger than ischaemic stroke survivors, with younger patients also facing higher risks of poststroke dementia than older patients. Given the higher societal burden of early-onset dementia, younger survivors of ICH therefore represent an important target for planning dementia prevention strategies in the future.

In the LATCH COG cohort, it is important to note that cognitive impairment and dementia were classified based on medical records alone. In a recent study of 738 patients who had experienced ICH, the modified Telephone Interview for Cognitive Status test determined that 19% of patients developed dementia within 6 months (Biffi et al, 2016). A total of 435 patients without dementia at 6 months were then followed up longitudinally (median follow-up 4 years), with an estimated yearly incidence of dementia of 5.8%, corresponding to 32% of patients being diagnosed during follow-up. This number is significantly higher than the incidence seen in LATCH COG, suggesting that the prevalence of cognitive impairment and dementia after ICH may be higher than that demonstrated for my cohort (see further discussion of accuracy of GP records in section 12.1.6). Despite this, adequate communication of the risk of cognitive decline, especially beyond the immediate period after ICH, is essential if we are to prepare patients, their family members and caregivers for the potential long-term effects of ICH.

11.1.5. Factors associated with new-onset cognitive impairment and dementia

In univariate analysis of LATCH COG, modified Rankin score >2 was associated with new-onset dementia 1-5 years after ICH. This first finding adds to those of Garcia et al (2013) who determined that Rankin score >1 at discharge, haemorrhage volume and discharge to a nursing home were all associated with long-term dementia (median time since ICH 40 months), suggesting that the severity of the acute ICH predicts future cognitive outcome. However, presence of posterior white matter lucencies (hypodensities on CT) was also associated with new-onset dementia in univariate analysis of LATCH COG, indicating an association between markers of small vessel disease and risk of developing new-onset dementia. In a study of 50 ICH survivors (median time since ICH 3.8 years), cognitive

impairment- as defined by a MoCA score of <24- was associated with leukoariorosis score (presence of posterior and anterior white matter lucencies) in univariate analysis (Tveiten et al, 2014). In a more recent study of the risk factors associated with early vs delayed dementia after intracerebral haemorrhage, CT-defined white matter hypodensity was associated with delayed (onset after 6 months) post-ICH dementia (Biffi et al 2016). The authors could not exclude the possibility that pathological processes of Alzheimer's disease had played a role in the observed findings. Certainly, SVD related markers- such as white matter abnormalities- have been previously observed in patients with Alzheimer's disease (Brickman 2013).

In line with my findings for pre-existing cognitive decline, in Cox regression analysis of LATCH COG, patients who had a lobar ICH were twice as likely to exhibit new-onset cognitive decline than those who had a non-lobar ICH. In those who survived past 30 days, the incidence of new-onset cognitive decline was 37% in patients with lobar ICH and 20% in patients with non-lobar ICH. The most immediate assumption is that an underlying cerebral amyloid angiopathy is contributing to the risk of cognitive decline after ICH (Tvieten et al 2014; Moulin et al 2016). CAA has been shown to be associated with both cognitive impairment and lobar ICH (Banjeree et al, 2018). CAA is a common small vessel disease of the brain, characterised by the deposition of amyloid β protein in the walls of small to medium sized arteries. Population-based autopsy studies have indicated CAA in 20-40% of non-demented patients, 50-60% of demented elderly patients, and more than 90% of patients with Alzheimer's disease (Charidimou, Gang and Werring 2012). Moreover, cerebral amyloid angiopathy is not thought to extensively contribute to vascular dementia, suggesting that an Alzheimer's disease degenerative process could be associated with lobar ICH (Thal, Grinberg and Attems 2012; Moulin et al, 2016). However, it is also worth noting that lobar ICH is more likely to affect cortical functions than non-lobar ICH, which might consequently affect cognition. The only factor associated with new-onset dementia in Cox regression analysis of LATCH COG was increasing age (Tvieten et al 2014; Moulin et al 2016).

In the LINCHPIN COG cohort, new-onset cognitive impairment at 6 months was associated with pre-ICH history of hypertension (p .001). Although hypertension is common in both patients with and without poststroke cognitive decline, all participants with new-onset cognitive impairment in my study suffered from pre-ICH hypertension. This implies an important role of vascular processes on the pathophysiology of post-ICH cognitive decline. This would coincide with the findings of numerous studies that have demonstrated that

hypertension increases the risk for cognitive impairment, vascular dementia and Alzheimer's disease (Aronow 2017). Cerebral blood vessels are the main target of the effects of hypertension on the brain. The resulting structural and functional cerebrovascular alterations underlie many of the neuropathological abnormalities responsible for the cognitive deficits, including white matter damage and brain atrophy (Pantoni 2010). Although my findings would support the reduction of cognitive impairment by antihypertensive drug therapy, the link between hypertension, its treatment and cognition remain poorly understood (Iadecola et al, 2016).

11.1.6. Accuracy of GP medical records for identifying cognitive impairment and dementia

In the LATCH cohort, pre-existing and new-onset cognitive impairment and dementia were classified based on medical records alone however, an IQCODE was available for 132 of these patients. The IQCODE formed part of the clinical assessment in LINCHPIN, and therefore its use is limited to those who gave written informed consent. This number is further limited by the substantial number of participants who either died soon after admission, when it was not appropriate to approach a close relative for completion of a questionnaire. When the IQCODE was compared to medical records for the detection of pre-existing cognitive impairment or dementia, screening of medical records alone did not detect 10 cases of dementia (although 6 were recorded as having cognitive impairment) and 27 cases of cognitive impairment, which is in keeping with reported under-recording of dementia diagnosis in primary care (Iliffe et al, 2009). Although I tried to correct for this by hand searching of the entire GP consultation record including individual consultation records and all hospital clinic and discharge letters to look for evidence of cognitive impairment satisfying the DSM-IV criteria for dementia, the prevalence of cognitive impairment and dementia may still be higher than that demonstrated for this cohort.

Half of the patients with pre-existing dementia had been previously diagnosed by their GP, which is in line with findings from Iliffe et al (2009) and Connolly et al (2011). In their narrative review, Iliffe et al (2009) state that dementia is probably underdiagnosed and under treated with an estimated 50% of primary care patients over the age of 65 not diagnosed by their GP. Similarly, Connolly et al (2011) found that the prevalence of dementia amongst patients 65

years and over identified using GP dementia registers was less than half that expected based on epidemiological data. Underdiagnosis of dementia occurred across all regions involved in the study (six Primary Care Trusts across Greater Manchester; 351 GPs; 1.8 million patients), suggesting that it is probably happening elsewhere in the UK.

Previous research has shown that dementia diagnosis may be missed by carers, patients and professionals because symptoms and loss of daily living skills are often misconstrued as part of the normal aging process (Iliffe 1997). It might also be the case that new-onset dementia in my study population was misconstrued as a normal consequence of the stroke. This study adds to existing evidence of the current and ongoing underdiagnosis of dementia in primary care. Given that almost two-thirds of adults with ICH are aged 75 years or older, its incidence is likely to become more prevalent in our aging population. Further research should therefore focus on understanding the factors that lead to underdiagnosis to ensure that the gap between those who are diagnosed and those who are missed does not get wider. Otherwise, with the growing elderly population, increasing numbers of patients will be denied access to potentially beneficial treatment and support.

Regarding pre-existing cognitive impairment with no dementia, the results are also worrisome. Although frequent (one ICH patient out of three with an available IQCODE had cognitive impairment with no dementia), only a few patients could be identified with having cognitive impairment in their medical records. Of those patients with an IQCODE score indicative of cognitive decline (37 patients), 27 were recorded as having no history of cognitive decline in baseline characteristics, 6 as having cognitive impairment (no dementia) and 4 as having dementia. These patients are at high risk of developing poststroke dementia therefore clinicians might need to pay close attention to cognitive status in patients with intracerebral haemorrhage (Henon et al 2001).

11.1.7. Correlation of cognitive impairment with assessments of functional outcomes

I could not detect statistically significant associations between new-onset cognitive impairment and any of the measures of functional outcome at 6 months. The small sample size may have been a significant contributory factor, making it difficult to identify any statistically significant differences between those with and without cognitive impairment.

EQ-5D is an instrument for measuring HRQOL across five different domains: Mobility; Self-care; usual activities; Pain/discomfort; Anxiety/depression. From the results in the five dimensions, an index value was derived. At 6 months after the ICH (in those without pre-existing cognitive decline), mean VAS was 77 and the mean utility score was 0.68. No participants had a utility score <0 (HRQOL worse than death); 3% a utility score <0.2; 20% a utility score <0.5; and 60% a utility score <0.8 (average score in general population of UK). On the other end of the scale, 9% had a utility score of 1 (perfect HRQOL).

Although ICH patients were more likely to report problems in each of the five domains on the EQ-5D than the general population, the EQ-5D utility score was only slightly lower than population norms for the UK (for ages 75 and above). It is also worth noting that while 49% of ICH patients reported having problems with anxiety/depression in the EQ-5D, PHQ-9 scores were below the cut-off for depression, with only 17% of participants reporting problems with mood and going beyond the initial screening questions. These findings suggest that problems with health-related quality of life and functional outcome questionnaires go beyond that of not being able to obtain statistical significance and may also have something to do with the inadequacy of the tools that were selected for the assessment of these outcomes (further discussion provided in section 11.1.8).

To date, only two studies have assessed HRQOL after ICH and its clinical predictors (Chrsitensen, Mayar and Ferran 2009; Delcourt et al, 2017). Analysis from the Factor Seven for Acute Haemorrhagic Stroke Treatment (FAST) trial showed that low overall HRQOL- as measured by the EQ-5D utility score in 621 patients at 90 days after their ICH- was associated with age, clinical factors (stroke severity, systolic blood pressure (BP) and neurological deterioration) and imaging features (larger and deep ICH). However, individual HRQOL dimensions within the EQ-5D were not reported. At 3 months after the ICH, mean VAS score was 62.2 and the mean utility score was 0.62. Although the EQ-5D scores are lower than that reported in LINCHPIN COG, participants were significantly younger (mean age 64 years).

The INTERACT study aimed to determine baseline factors associated with HRQOL in 2756 patients using the EQ-5D at 90 days, completed by patients or proxy responders. Like the findings of LINCHPIN COG, median utility score was 0.7. The distribution of EQ-5D utility scores was left skewed, with 1251 patients having a utility score equal or lower than the median (≤ 0.7), and 1505 patients with a utility score higher than the median (> 0.7). Higher

NIHSS score (≥ 14), larger ICH and use of proxy responders were associated with problems in all five dimensions of the EQ-5D. Neither of the studies recorded participant's cognitive status, therefore no previous data exists on the associations between cognitive impairment and HRQOL after ICH.

11.1.8. Measuring HRQOL

As discussed in Chapter 1, there is no universally accepted definition for the term HRQOL. However, there is a substantial body of literature devoted to discussing and identifying important domains to be included. The theoretical framework of HRQOL was essentially developed to give a multidimensional perspective of health as a combination of physical, psychological and social functioning. These domains have since formed the basis for the development of psychometric tools to measure health-related aspects of an individual's quality of life. Tools are generally developed to be either disease specific or generic measures of HRQOL, where data are typically collected using checklists or scaling devices. Although the use of such questionnaires has potential benefits- including richer information about patients and an improved awareness of the personal and social consequences of illness- they may not produce results that are meaningful (for example, what does a utility score of 0.6 really mean?) (Fitzpatrick 1999). Carr and Higginson (2001) point out that simply listing quality of life domains is not a satisfactory way of measuring quality of life as it is not known whether all the important domains have been covered. The challenge of measuring quality of life lies in its uniqueness to individuals. They suggest that many of the existing measure of health-related quality of life fail to take this into account, imposing standardised models of quality of life and pre-selected domains, thus measuring general health status rather than health-related quality of life.

Although an impressive body of work has been developed around HRQOL and recovery following stroke using (almost exclusively) standardised HRQOL questionnaires, serious concerns have been raised about the extent to which these measures reflect the experiences and perspectives of patients. As stated by Dowswell et al (2000):

"Lives encompass more than physical function; they are a complicated mesh of roles, relationships, activities and perceptions." (p. 514).

Improvements that are measured through instruments such as the EQ-5D may therefore not be regarded as significant by the stroke patients themselves. The most frequent criticism of the EQ-5D is its lack of responsiveness to change (likely due to a ceiling effect), however this was addressed with the restructuring of the EQ-5D to include five levels of severity (prior to this there had only been three) (Wu et al, 2002). Although the EQ-5D would appear to provide rather crude insights into HRQOL and its recovery among survivors of critical illness, it remains one of the most widely used measures within health research and has been administered and validated for use among a diverse range of patient populations, including stroke (Golicki et al, 2015) and dementia (Hounscome, Orrell and Edwards 2011).

Health-related quality of life data can provide important information concerning the impact of chronic illness on the lives of individuals. A great deal of research has been conducted using a qualitative approach to assess the quality of life of stroke survivors. Prevalent criticisms of a qualitative approach include its *"impressionistic"* and *"unscientific"* nature (Bryman 1984, p79) and the specificity of findings to the individuals or settings involved (i.e. limited generalisability). As such, researchers in the field of quality of life research are now suggesting that a combination of questionnaires and interviews may be a more appropriate way of exploring the health-related quality of life of patients (Clarke 2009). Although there is limited guidance available on the use of a mixed methods approach to HRQOL, a primary concern in this research is that of merging analyses of quantitative and qualitative data to provide an integrated analysis (Bryman 2007). Certainly, guidance on how to present mixed methods findings in such a way that the quantitative and qualitative findings are genuinely integrated is lacking among the literature in this field. This thesis therefore provides an opportunity for the researcher to contribute to the methodological debate on the usefulness of these measures (and their combination) in assessing the health-related quality of life of patients.

When considered at group level, the numerical data produced by the functional outcome questionnaires could easily give the impression that cognitive impairment after ICH had a negligible impact on patients' quality of life. The data also seems to suggest that cognition neither improved nor got worse over the stroke trajectory (6-24 months). Means such as these that stay the same can easily mask decreases at an individual level. Contrary to the quantitative data, interview data quite clearly demonstrated the devastating effects that stroke due to haemorrhage can have on the lives of survivors and their families. Although the

small sample size would have made it difficult to identify any statistically significant differences between those with and without cognitive impairment, it seems as if the problem with quality of life questionnaires goes beyond that of not being able to obtain statistical significance.

While the scores on the functional outcome assessments indicated a particular trend, on their own they were relatively meaningless, requiring further descriptive information in order to interpret and explain them. Because of this problem, the tools alone appear to offer little understanding of the impact of stroke due to haemorrhage on the quality of patients' lives in this study. One potential reason for the mismatch of scores against the interview data could be that the questionnaires asked participants to rate how they have been feeling over the last week/two weeks (dependent on scale), whereas the interviews allowed for a much broader coverage, going back to stroke onset. Another reason could be that the questionnaires were answered prior to the interviews; ratings may have been more accurate after an exploration of the issues. Interview material also indicated that for these participants, quality of life was a much broader concept than the criteria expressed in the generic functional outcome questionnaires. In effect, the use of the in-depth interviews allowed a greater exploration of experiences, in a more comprehensive way than would have been possible relying on HRQOL and functional outcome questionnaires alone.

11.1.9. Life after stroke- biographical disruption

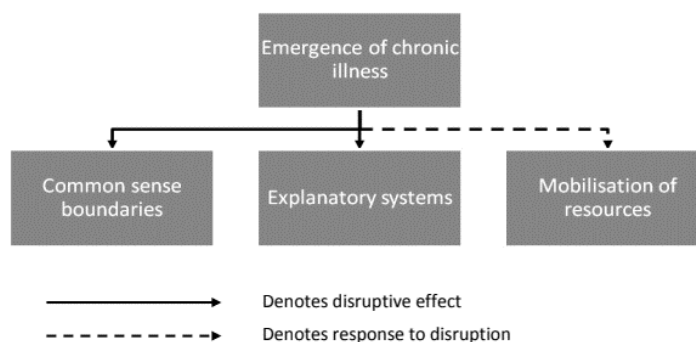
Some authors have suggested that the experience of stroke represents a continuity with patient's previous lives, where individuals are resilient in finding ways to maintain valued life activities (Atchley 1989; Pound, Gompertz and Ebrahim 1998). However, for the sample in this study, experiences were predominantly negative, where the stroke represented a clear discontinuity with a previous way of life. In this way, the stroke can be seen to represent a major biographical disruption in the lives of patients and family members. The reporting of findings will therefore draw on biographically informed approaches to understanding chronic illness, particularly the work of Bury (1982) and Charmaz (1995), to explore the extent to which participants within the first two years following diagnosis experience stroke due to haemorrhage as biographically disruptive.

Biographical Disruption:

The notion of illness as biographical disruption is attributed to Michael Bury (1982) and represents a significant turning point in our understanding and conceptualisation of experiences of chronic illness. In his classic paper, Bury (1982) reported on his work with newly diagnosed rheumatoid arthritis sufferers. For this study, participants were selected to allow the impact of the emerging illness to be explored. Bury criticised the assumption underlying the Parsonian concept of the sick role which viewed illness/disablement as a relatively stable condition. Bury's approach argued that a person with a chronic illness has a more fluid trajectory, which includes periods of adaptation and other periods where symptoms were more pervasive (for example, after a surgical episode or sudden exacerbation of symptoms). The concept of biographical disruption therefore acts as both a descriptor of people's experiences as well as an explanatory device to comprehend how people respond and adapt to chronic illness. Although biographical disruption is a multi-faceted process, Bury (1982) reveals three sequential aspects of disruption (see Figure 25; reproduced from Ramsay 2010):

- The disruption of taken-for granted assumptions about our bodies, selves and the social world in which we live.
- Profound disruptions in the explanatory systems normally used by people, such that a fundamental re-thinking of the person's biography and concept of self is involved.
- The response to disruption involving the mobilisation of resources.

Figure 25: Stages of Biographical Disruption



Stages:

Disruption to 'common sense boundaries' refers to an event (such as chronic illness) that brings to the fore a:

"recognition of pain and suffering, possibly even death, which are normally only seen as distant possibilities or the plight of others" (Bury 1982, p.169)

The emergence of chronic illness elicits both a raised awareness of one's previously 'invisible' and normally functioning body and disrupts the sense of unity between body, self and one's identity (Charmaz 1995). Like Bury, Charmaz (1995) suggests that chronic illness compels people to have an awareness of death. She emphasises how this disrupts their identity, particularly if the individual defines themselves as healthy and had no previous experience of illness.

The second disruption to pre-illness 'explanatory systems' relates to the ways in which individuals have to re-consider their own concept of self and identity. This stage tends to raise questions of a 'why me, why now?' nature in relation to causality. Importantly, Bury's respondents were ultimately confronted by the limitations of a scientific explanation and medical intervention, most notably in terms of how to live with their debilitating illness. Among Bury's younger respondents, uncertainty in relation to the aetiology and legitimacy of symptoms was often compounded by the common cultural paradigm of arthritis as a disease associated with the ageing process. On the other hand, those respondents who were invariably older attributed the disease process to 'normal wear and tear'.

The third stage- 'mobilisation of resources', relates to the adaptive response of the individual to the disruption, in light of their differing circumstances. The response to disruption comprises the mobilisation of resources- physical, social, financial, medical etc- available to the individuals and their family. Bury's (1982) work is largely descriptive here and somewhat limited in scope.

Biographical disruption, in summary, constitutes:

“...a useful concept, shedding important sociological light on the nature of chronic disabling illness and the coping processes, practical strategies and symbolic styles of adjustment it calls forth.” (Williams 2000, p.49)

Bury developed his theory further by identifying two distinct types of meaning; the practical *consequences* for the individuals (in terms of the impact and management of the symptoms on everyday life) and the symbolic *significance* (different conditions carry with them different connotations and imagery) attributed to the illness by the individual (Bury, 1991). Bury also differentiated between three aspects of adaption that individuals can draw upon to manage their level of disruption. ‘Coping’ refers to the methods the ill person uses to manage his or her situation emotionally. ‘Strategy’ refers to the way in which the ill person tries, through his or her actions, to deal with illness. ‘Style’ reflects how different people have different attitudes towards illness” (Hubbard and Forbat, 2012, p2034).

Importance of context:

In recent years, other researchers have extended Bury’s analysis or critically developed work in a similar vein. In arguably the most authoritative critique of Bury’s construct, Williams (2000) argues that:

“Biographical disruption cannot simply be assumed or “read off” as a standard response, with similar effects, to a similar event, illness-related or otherwise” (Williams; 2000: 54).

Put simply, the experience of illness as biographically disruptive differs depending on the context; where the disruptive effects of illness may be mediated by the timing and normality of various illnesses (Williams, 2000).

The importance of age and stage in the life-course at which a person becomes unwell has been a central theme within much of the work that sought to revisit Bury’s (1982) concept of biographical disruption. The participants in Bury’s original project were relatively young, recently diagnosed rheumatoid arthritis sufferers. Bury (1982) pointed to the age of his participants and the stereotype of rheumatoid arthritis as being a disease of the older generation in order to present one explanation for why they experienced the onset of the

disease as being so disruptive. In applying the concept to different populations of varying ages, research has demonstrated discrete differences to Bury's original work (Pound, Gompertz and Ebrahim 1998; Sanders, Donovan and Dieppe 2002). In a sample of predominantly elderly stroke patients (from a predominantly lower socioeconomic background), all respondents described the considerable ways in which the stroke had impacted on their lives. However, the majority of those interviewed viewed the stroke as a normal part of their biographical trajectory- or a 'normal crisis' in their 'hard-earned lives'- and played down its significance (Pound, Gompertz and Ebrahim 1998). A similar observation was made by Sanders, Donovan and Dieppe's (2002) elderly respondents who perceived the highly disruptive effects of osteoarthritis on their daily lives as a 'normal', and a biographically anticipated aspect of the ageing process. In this study, the rate of disease deterioration was found to impact on the level of biographical disruption experienced (Sanders, Donovan and Dieppe 2002).

Additionally, the presence of co-morbidities has been shown to reduce the amount of disruption experienced by individuals as they are likely to be accustomed to the illness role and thus already lead restricted lives (Pound, Gompertz and Ebrahim 1998). Carricaburu and Pierret (1995) make a similar observation in their exploration of the experience of illness of asymptomatic HIV positive men who were infected either through medical treatment for haemophilia or same sex relations. While those infected because of same sex relations tended to experience HIV as biographically disruptive, many of the haemophiliacs had already organised their lives and biographies around an illness trajectory and were used to living their lives in the face of uncertainty. As such, an HIV diagnosis served as what Carricaburu and Pierret (1995) coined 'biographical reinforcement'. We cannot assume that all chronic illness is experienced as a 'shattering' of our taken-for-granted assumptions about our bodies and selves. In doing so:

"we fail to account for a range of other possibilities in which illness may already be a central part of one's biography" (Williams 2000, p. 60).

It is clear from the literature that the type of illness can also affect the level of biographical disruption experienced by patients. For example, those diagnosed with conditions perceived to have elements of stigma attached to them (e.g. epilepsy) appear to experience greater biographical disruption (Scrambler 2009). Alternatively, conditions such as arthritis which are

perceived as a natural progression of ageing, are more likely to be attributed to a 'normal' biographical trajectory (Sanders, Donovan and Dieppe 2002). Whether a chronic illness is suffered as a biographical disruption therefore depends on multiple context-dependent contingencies. As stated by Pound, Gompertz and Ebrahim (1998), the key issue highlighted in these papers is:

"the importance of contextualising illness, both within the life of the individual and the collective to which they belong" (p.491).

11.1.10. Effect of stroke on sense of self and identity

Numerous sociological studies have illustrated the impact that chronic illness can have on someone's sense of self and identity (Charmaz 1983). Self can be seen as the product of a person's own attributes (goals, aspirations, experiences, interests, behaviours etc). It is separate from identity, which relates to how an individual defines, locates, and differentiates the self from others. Identity implicitly takes into account the ways people *wish* to define themselves (Charmaz 1995). According to Charmaz (1983), 'loss of self' is experienced by people with chronic illness because their former lives and selves are precluded by illness. Drawing upon her experience of working with people with a variety of chronic illnesses and who were severely disabled or housebound, Charmaz (1983) developed the concept of 'loss of self' to describe the participants experience of:

"former self-images crumbling away without a simultaneous development of equally valued new ones" (p168)

In several of the interviews, participants perceived that they were no longer the person that they were before the stroke, suggesting that a disruption to their sense of self had occurred. This was often due to changes in their physical and cognitive dispositions. Physical and cognitive disability as a result of stroke can be problematic for an individual's sense of self and identity if they limit the person's ability to return to activities that were integral to their prestroke lives.

Compared to older persons, young people (below retirement age) who have a stroke are more likely to survive their initial illness and live for many years with functional or cognitive

deficits that impact their daily living (Varona et al, 2004). Adults who are in the midst of working and raising children may experience a particularly profound diversion from their anticipated life trajectory. In a literature review of qualitative studies exploring the experience of stroke from the perspective of younger adults (18-65 years old), Lawrence (2010) unearthed three main themes: disorientation; a disrupted sense of self; and altered roles and responsibilities. Many of the effects of stroke (such as cognitive impairment) are 'invisible' but have significant impacts on relationships and social participation, including the ability to return to work and to enjoy an active social life. Lawrence's findings lend support to Bury's (1982) work which found that diagnosis of a chronic illness at a young age left individuals feeling shocked and confused. Stroke at a young age marks a significant divergence from the life trajectory that individuals perceived themselves to be on prior to their diagnosis. Although the shock of diagnosis and symptoms can be hard at any age, research by Pound, Gompertz and Abraham (1998) suggests that older age can sometimes serve as a buffer, as chronic illness may be expected as a normal part of the aging trajectory. Lawrence (2010) also found that altered roles and relationships emerged when individuals felt that they were a burden to others. Similarly, Charmaz (1983) found that following chronic illness, people tended to lead a more restricted life, became socially isolated and felt that they were a burden to others.

The notion of 'burden' was commonly found within the transcripts analysed. As well as reporting the burden of illness upon themselves, participants often felt as if they were becoming a burden to friends and family as a result of their condition. Participants frequently reported not wanting to worry or concern family members about their health. In my study, burden was particularly marked within participants' relationships with their family (spouse and children) and was most significant amongst women. Burden is a theme commonly found within the literature on terminal and chronic illnesses (Cousineau et al, 2003; McPherson et al, 2007). Self-perceived burden in this way has been defined as:

"empathic concern engendered from the impact on others of one's illness and care needs, resulting in guilt, distress, feelings of responsibility and diminished sense of self." (McPherson et al, 2007 p. 425)

This definition has been chosen as it proposes a psychological construct not linked to dependence, as people could feel like they were a burden even when they were not

dependent on others. The feeling of being a burden had clear implications for participant's social interactions, relationships, and mood.

Several theoretical perspectives on stroke recovery have emerged over recent years. A key concept in much of this work has been centred around the idea of loss, whereby the lives of stroke patients and family members are turned upside down. Patients lose physical functions, social networks, activities, suffer cognitive decline and sometimes lose their sense of self and identity. Individuals can combat biographical disruption by either adapting to the disrupted identity or accepting it and establishing a new identity in the process (Locock et al, 2009). This echoes the work undertaken by Corbin and Strauss (1991) on the process of overcoming disability through comeback, which refers to returning to a satisfactory way of life, within the physical/mental limitations imposed by a disabling condition.

11.1.11. Adaption and adjustment

Individual approaches to adaption and adjustment can minimise the effects of disability on the person's sense of identity. Bury's (1991) concept of coping is particularly relevant here as it refers to the ways in which individuals manage the level of disruption. It involves:

"maintaining a sense of value and meaning in life, in spite of symptoms and their effects" (Bury 1991 p. 461)

Similarly, Williams (1984) uses the term 'narrative reconstruction' to describe how individuals with chronic illness establish a sense of order and meaning in their lives over time. Adapting implies that the individual acknowledges their impairments and alters their life and self in socially and personally acceptable ways (Charmaz 1995). While some survivors employed strategies to keep their pre-illness lifestyle intact by maintaining as many pre-illness activities as possible (even in a modified way), others found ways to incorporate their illness into an altered lifestyle. Specific elements of adaption included other family members or friends taking on tasks for them, individuals learning to cope without being able to drive, or learning to do tasks and activities at a lower level or frequency.

Both Bury (2001) and Charmaz (1995) describe some of the biographical work that individuals undertake to regain, restore and preserve a pre-illness sense of self. Bury (2001) emphasises

the importance of people trying to normalise their lives by keeping their pre-illness lifestyle and identity through the maintenance of pre-illness activities. However, the journey towards recovery often involved overcoming various perceived barriers. None of the participants in the study had been able to return to their paid employment following their stroke. For many, their job had given them a sense of value and meaning in life, both of which were now being threatened with the onset of chronic illness (Bury 1982). Although returning to work would have brought about a sense of normality, unfortunately for the participants in the study, there appeared to be a lack of genuine support and understanding in relation to employment. This reinforces Bury's (1982) finding regarding the importance of 'external resources' to the ways in which illness and experience is lived out. This is also highlighted in Hart's (2001) study of 'system induced setbacks' in stroke recovery. Hart (2001) emphasised the ways in which setbacks in stroke recovery can appear to be due to a problem with the patient (at least from a medical perspective), but in reality often result from a problem with the health and social care systems put in place in the aftermath of stroke.

Access to supports and resources is essential for enabling stroke survivors to engage in adaptive strategies. As highlighted by Bury (1982), the onset of disease not only disrupts structures of meaning, but also relationships and practical affairs. Stroke can often lead to a growing dependency on the help of others, where the strength of the person's social network (for example, how supportive family, friends and colleagues are willing to be) and their ability to mobilise physical resources become crucial to the ways in which the illness is subsequently experienced. In the interviews, participants spoke about the importance of health and social services, family members and peers for the provision of emotional and instrumental supports that assisted them in their everyday lives. Working-age stroke survivors suffered disruption to their identities and abilities in relation to age-appropriate roles, such as employment. For those younger survivors who were interviewed, recovery goals often related to raising children, re-arranging finances, employment and spousal relationships (Lawrence 2010; Morris 2011). From the interviews however, it became apparent that services in the community (including physical rehabilitation) were predominantly geared towards the older age group. Stroke survivors need to feel supported if they are to achieve their best possible, individual, quality of life.

11.1.12. Uncertainty

The notion of uncertainty as a form of disruption is a common theme within research on the experience of chronic illness (Bury 1982). For many, uncertainty began at stroke onset. Within the interviews, the direct relationship between stroke, bodily sensation and communication is evident. As the individuals started to feel the effects of having a stroke, an internal dialogue often began between the body and self (Faircloth, Boylstein, Rittman and Gubrium 2005). For example, as symptoms started to appear (e.g. weak arm/leg, loss of speech) many of the participants knew in their mind that something wasn't right but couldn't quite figure out why their bodies were responding in such a way. The separation of mind and body that occurs during the stroke event is often continued into the stroke trajectory as participants start to question why their bodies can no longer function as they could before the stroke. There may be intrusive symptoms such as pain; there may be interruptions to usual physical and social routines; and there may be cognitive disorientation or confusion (Kelly and Field 1996). Having a serious chronic illness like stroke can therefore be seen to disrupt the taken-for-granted assumptions that individual's make about possessing a smoothly functioning body. As pointed out by Charmaz (1995), this was particularly evident when individuals defined themselves as previously fit and healthy.

A major issue which seems to have emerged from the study is the need to review the meaning and experience of the term 'recovery'. The Oxford dictionary definition of the term 'recovery' refers to *'A return to a normal state of health, mind, or strength'*. However, this is rarely possible when it comes to life after stroke. Patients and caregivers provided vivid descriptions of the recovery process. Recovery was often perceived in terms of personal factors and prestroke lives, with participants therefore having very individual and diverse measures of their recovery.

Recovery across time following stroke involves transitions. Here, we define transition is a *"passage from one life phase, condition or status to another"* and is usually precipitated by a triggering event (Chick and Meleis 1986, p.239). Stroke is a triggering event with initial concerns centred around survival. Once the initial onset and impact of the stroke have occurred, individuals begin to face the longer-term implications of their altered circumstances (Bury 1991). As previously discussed, all participants experienced changes in their bodies, both soon before hospitalisation and after being diagnosed with the stroke. The changed body was directly related to many different aspects of the participant's experience,

such as their relationships with others, their roles and identities, their jobs, their physical and functional limitations, and their ability to cope and manage with life after stroke. Thus, the experience of transition from hospital to home is greatly influenced by the bodily changes post stroke.

The transition from hospital to home following a stroke is a critical period in the recovery trajectory. Survivors must learn how to manage their functional limitations within the context of their family and home (Rittman et al, 2004). Survivors often receive vague medical responses to concerns over the uncertainties of recovery. Uncertainty was therefore exacerbated by a perceived lack of information about prognosis and chronic illness management. While stroke survivors adapt to their illness over time, they continue to experience impairments and disruptions in their personal and work lives. To understand the meaning of recovery, the physician must understand what is important and valued by the person. Treatment strategies and poststroke education therefore need to address the concerns of the survivor within their social context. In addition, a holistic model of rehabilitation that helps individuals regain the capacity for everyday activities related to work, family life and leisure is needed if we are to help survivors restore wellness and work towards minimising the burden felt by family members.

Bury (1991) argues that only the passage of time and trial and error provide the mechanism for re-establishing some form of certainty. Indeed, processes of adaption and adjustment are likely to become more successful over time. As such, examples of participants establishing some form of certainty and regaining control of their lives may be less visible in my study since the strokes had all occurred in the 2 years prior to interview. Frequent interviews collecting data from a larger sample of stroke survivors over repeated periods of time are therefore needed to explore the impact of time on uncertainty and notions of recovery.

11.1.13. Life after stroke for family members

The sudden nature of stroke tends to place family members into the role of carer with little or no warning or preparation (Smith et al, 2003). Family members reported feeling abandoned by services but did not have the knowledge or skills to re-engage. A lack of continuity of care: including lack of active follow-up, limited and delayed access to community services, as well as inadequate information about stroke, recovery and healthcare services, left individuals and family members feeling frustrated and dissatisfied.

A need for information or skills training seemed to be a major issue for family members and has been consistently reported as an unmet need in previous studies (Brereton 2002; Cecil et al, 2010). There is a clear demand for the provision of timely and targeted information about stroke and available resources, as well as a need for regular follow-ups (either from primary care or hospital) from healthcare professionals.

Caregivers and family members may benefit from understanding that as the stroke survivor manages the transition period from hospital to home, not only are they testing their functional capabilities, but their sense of self and identity is changing at the same time. Family members and caregivers need to support the stroke survivor as they attempt to regain participation in a meaningful role in the family (Rittman et al, 2004).

11.2. Clinical implications

This study found a substantially higher rate of cognitive impairment in ICH patients than would be expected in an age-matched general population. Cognitive impairment before ICH is common and is associated with imaging findings consistent with a contribution from cerebral amyloid angiopathy. For those without pre-existing dementia, more than 2 out of every 5 patients will exhibit new-onset cognitive decline at 6 months. My findings are of clinical relevance in the management of ICH survivors and will allow patients and family members to be adequately informed about the risk of cognitive decline.

Stroke rehabilitation tends to be concentrated in the first 6 months following a stroke, but data from my research highlight that stroke recovery is a much longer process, characterised by periods of uncertainty. A survey conducted by the Stroke Association in the UK found that services are lacking after patients are discharged from hospital (Stroke Association 2012). Half of the individuals who were surveyed had only been assessed once after being discharged from hospital, with coordination of care falling to the family. There is a need to acknowledge that patients want and require a variety of services which must be finely tailored to meet their individual needs as they arise. Patients should be assessed systematically to determine their information deficits and agreed interventions should be put in place to meet these needs, at the appropriate time that it is required (Smith et al, 2003). Understanding the long-term impact of stroke and the strategies that individuals use to

restore their lives can help inform the design of person-centred approaches to care and rehabilitation, ultimately helping to restore a sense of wellness.

This study also highlights the need for suitable interventions to support carers. Support for carers should focus on increasing understanding and management of the stroke. Nurses must address the needs of carers alongside the needs of stroke patients and provide appropriate support to family members involved in their care. The need for information on all aspects of stroke- diagnosis, prognosis, potential long-term outcomes and what to expect as a carer- stood out as a major concern, and one that clinicians and nurses must continue to address.

To the researcher's knowledge, this is the first study to explore patients' and family members' experiences of living with cognitive impairment following stroke due to haemorrhage. Experiencing a stroke and its aftermath can be devastating for patients and their families, and may be associated with severe physical, social and psychological consequences for patients. The emotional impact of stroke is unpredictable and requires ongoing attention throughout the years following the stroke. There is a need for ongoing psychosocial support for survivors and their families, including strategies to help individuals re-engage in their social networks. Greater efforts should be made to support people to return to paid employment, continue with daily household tasks and participate in social activities, if this is what they want to do. A holistic model of rehabilitation that helps individuals regain the capacity for everyday activities related to work, family life, and leisure, can begin to address the emotional ramifications of the stroke, restore quality of life and work towards minimising the burden felt by family members.

It is also worth noting the age of interviewees. The qualitative interviews tended to explore the experiences of younger, higher functioning stroke survivors as they re-established their identity and attempted to return to their prestroke roles, responsibilities and activities. Many individuals identified themselves through their work and leisure activities and were at a loss when these activities were no longer possible. From the interviews, it was evident that the younger survivors of stroke valued age-appropriate, identity-affirming goals, such as resuming employment. Return-to-work rehabilitation pathways could play a much greater role in supporting survivors' resumption of valued life roles (Wolfenden and Grace 2015). Some of the participants identified a need to belong among peers and individuals who understood the enormity and significance of their specific recovery challenges. Current

stroke support groups were not perceived as suitable for the needs of survivors in my sample. Stroke peer groups geared towards the specific needs of younger, higher functioning survivors on their recovery journey were identified as desirable, although not easily found.

11.3. Unanswered questions and directions for future research

Cognitive impairment is common both before and after ICH and has serious implications for experiences of life after stroke. Further research should investigate the impact of cognitive rehabilitation strategies using a mixed-method design that could combine patient perspectives with quantitative data.

There is a need for further mixed methods research into the experiences of younger, higher functioning stroke survivors. Interventions that assist people in navigating life changing circumstances and dealing with uncertainty might help maintain hope and should be tested with this population. Research is warranted on the impact of psychosocial interventions on recovery outcomes, unmet needs and experiences of anxiety and depression. Complex interventions can be guided by the Medical Research Council Framework, which directs the development, implementation and assessment of health-improvement initiatives (MRC 2000).

Implicit to some of the findings of studies exploring biographical disruption as a concept is the notion that the impact of chronic conditions on sense of self and identity is not static. Sense of self and identity are expected to change over time as individuals grasp new understandings of their situations. These new understandings can occur as a result of reflection over time as well as changes in physical conditions, or domestic and social environments. Although these changes are implied in biographical disruption literature, they have not been explored using a longitudinal methodological approach. This apparent gap in the existing literature suggests the need to adopt an approach capable of exploring changes to people's sense of self and identity over time, which may influence notions of recovery.

Further research is also required into finding ways to best help stroke survivors and families come to terms with the long-term consequences of stroke (Pollock et al, 2012). There remains a lack of interventions that address psychosocial symptoms that may hinder social and workforce participation (Lyons, Rudd and Alvaro 2007). Those who experience stroke as

a threat to identity may particularly benefit from interventions that support them to do effective biographical work to support them to retain as much of their pre-illness identity while also helping them to develop new identities in the context of their changing circumstances.

11.4. Conclusion

This thesis has addressed explicit questions about the long-term effects of intracerebral haemorrhage from the points of view of patients and family members. While the cohort study used standard, quantitative measures to determine the incidence of cognitive decline, its risk factors and the associations of cognitive decline with functional outcomes after an intracerebral haemorrhage, the qualitative interviews uncovered the devastating affect that a stroke due to haemorrhage can have on the lives of survivors and their families. Risk of cognitive impairment with intracerebral haemorrhage is a major concern for patients and family members, with participants often indicating that they could no longer be the person that they were before the stroke. By using both quantitative and qualitative methods, this study sought to gain a more comprehensive understanding of the outcomes and experiences of people living with cognitive impairment and intracerebral haemorrhage. The results of this study show a complicated picture of the difficulties faced by patients and family members in the two years following a stroke due to haemorrhage. Accepted instruments for estimating recovery are not comprehensive enough. By combining methodologies, we can avoid a simplistic or over-generalised assessment of functional outcomes, allowing differing perspectives of individuals to be taken into account.

References

- Adamit, T., Maeir, A., Ben, E., Assayag, N., Bornstein, M., Korczyn, A.D. and Katz, N., 2015. Impact of first-ever mild stroke on participation at 3 and 6 month post-event: the TABASCO study. *Disability Rehabilitation*, 37(8), pp. 667-673.
- van Agt, H.M., Essink-Bot, M.L., Krabbe, P.F. and Bonsel, G.J., 1994. Test-retest reliability of health state valuations collected with the EuroQOL Questionnaire. *Social Science & Medicine*, 39(11), pp. 1537-44.
- Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B. and Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers & Dementia*, 7(3), pp. 270-9.
- Al-Shahi Salman, R., Labovitz, D.L. and Stapf, C., 2009. Spontaneous intracerebral haemorrhage. *BMJ*, (339), b2586.
- Al-Shahi Salman, R., McGoohan, K., Rodrigues, M. and Dichgans, M., 2016. Dementia after stroke due to intracerebral haemorrhage. *Lancet Neurology*, 15(8), pp. 779-780.
- Altieri, M., Di Piero, V., Pasquini, M., Gasparini, M., Vanacore, N., Vicenzini, E. and Lenzi, G.L., 2004. Delayed poststroke dementia: a 4-year follow-up study. *Neurology*, 62(12), pp. 2193-2197.
- Alvarez-Sabin, J., Santamarina, E., Maisterra, O., Jacas, C., Molina, C. and Quintana, M., 2016. Long-Term Treatment with Citicoline Prevents Cognitive Decline and Predicts a Better Quality of Life after a First Ischemic Stroke. *International Journal of Molecular Science*, 17(3), pp. 390.
- American Psychological Association., 1994. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.: DSM-IV*. American Psychological Association: Washington, DC.
- Ankolekar, S., Renton, C., Sare, G., Ellender, S., Sprigg, N., Wardlaw, J.M. and Bath, P.M.W., 2014. Relationship between Poststroke Cognition, Baseline Factors, and Functional

Outcome: Data from 'Efficacy of Nitric Oxide in Stroke' Trial. *Journal of Stroke & Cerebrovascular Diseases*, 23(7), pp. 1821-1829.

Arauz, A., Rodriguez-Agudelo, Y., Sosa, A.L., Chavez, M., Paz, F., Gonzalez, M., Coral, J., Diaz-Olavarrieta, C. and Roman, G.C., 2014. Vascular cognitive disorders and depression after first-ever stroke: the Fogarty-Mexico Stroke Cohort. *Cerebrovascular Diseases*, 38(4), pp. 284-289.

Arba, F., Mair, G., Carpenter, T., Sakka E., Sandercock, P.A.G., Lindley, R.I., Inzitari, D. and Wardlaw, J.M., 2017. Cerebral White Matter Hypoperfusion Increases with Small-Vessel Disease Burden. Data From the Third International Stroke Trial. *Journal of Stroke and Cerebrovascular Diseases*, 26(7), pp. 1506-1513.

Ariensen, M.J., Claus, S.P., Rinkel, G.J. and Algra, A., 2003. Risk factors for intracerebral haemorrhage in the general population: a systematic review. *Stroke*, (34), pp. 2060-5.

Aronow, W.S., 2017. Hypertension and cognitive impairment. *Annals of Translational Medicine*, 5(12), pp. 259.

Arvanitakis, Z., Leurgans, S.E., Wang, Z., Wilson, R.S., Bennett, D.A. and Schneider, J.A., 2011. Cerebral amyloid pathology and cognitive domains in older persons. *Annals of Neurology*, (69), pp. 320-327.

van Asch, C.J., Luitse, M.J., Rinkel, G.J., van der Tweel, I., Algra, A. and Klijn, C.J., 2010. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurology*, (9), pp. 167–76.

Atchley, R.C., 1989. A continuity theory of normal aging. *The Gerontologist*, (29), 183-190.

Attems, J., Lauda, F. and Jellinger, K.A., 2008. Unexpectedly low prevalence of intracerebral hemorrhages in sporadic cerebral amyloid angiopathy: an autopsy study. *Journal of Neurology*, (255), pp. 70-76.

Bailey, R.D., Hart, R.G., Benavente, O. and Pearce, L.A., 2001. Recurrent brain haemorrhage is more frequent than ischaemic stroke after intracranial haemorrhage. *Neurology*, 56(6), pp. 773-777.

Banjeree, G., Wilson, D., Ambler, G., Appiah, K.O.B., Shakeshaft, C., Lunawat, S., Cohen, H., Yousry, T., Habil, M., Lip, G.Y.H., Muir, K.W., Brown, M.M., Al-Shahi Salman, R., Jager, H.R. and Werring, D.J., 2018. Cognitive impairment before intracerebral haemorrhage is associated with cerebral amyloid angiopathy. *Stroke*, (49), pp. 40-45.

Barba, R., Castro, M.D., del Mar Morín, M., Rodríguez-Romero, R., Rodríguez-García, E., Cantón, R. and Del Ser, T., 2001. Prestroke dementia. *Cerebrovascular Diseases*, 11(3), pp. 216-224.

Barba, R., Martínez-Espinosa, S., Rodríguez-García, E., Pondal, M., Vivancos, J. and Del Ser, T., 2000. Poststroke dementia: clinical features and risk factors. *Stroke*, 31(7), pp. 1494-1501.

Barker-Collo, S., Feigin, V.L., Parag, V., Lawes, C.M.M. and Senior, H., 2010. Auckland Stroke Outcomes Study: Part 2: Cognition and functional outcomes 5 years poststroke. *Neurology*, 75(18), pp. 1608-1616.

Baumgart, M., Snyder, H.M., Carrillo, M.C., Fazio, S., Kim, H. and Johns, H., 2015. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer's & Dementia*, 11(6), pp. 718-726.

Bejot, Y., Aboa-Eboule, C., Durier, J., Rouaud, O., Jacquin, A., Ponavoy, E., Richard, D., Moreau, T. and Giroud, M., 2011. Prevalence of early dementia after first-ever stroke: a 24-year population-based study. *Stroke*, 42(3), pp. 607-612.

Benedictus, M. R., Hochart, A., Rossi, C., Boulouis, G., Henon, H., van der Flier, W.M. and Cordonnier, C., 2015. Prognostic Factors for Cognitive Decline After Intracerebral Hemorrhage. *Stroke*, 46(10), pp. 2773-2778.

Beuscher, L. and Grando, V.T., 2009. Challenges in conducting qualitative research with persons with dementia. *Research Gerontological Nursing*, 2(1), pp. 6-11.

Biesta, G., 2010. Pragmatism and the philosophical foundations of mixed methods research. In Tashakkori, A. and Teddlie, C. (eds.) *Handbook of Mixed Methods in Social & Behavioral Research*. 2nd ed. London: Sage , pp. 95-118.

Biffi, A., Bailey, D., Anderson, C.D., Ayres, A.M., Gurol, E.M., Greenberg, S.M., Rosand, J. and Viswanathan, A., 2016. Risk Factors Associated With Early vs Delayed Dementia After Intracerebral Hemorrhage. *JAMA Neurology*, 73(8), pp. 969-976.

Bisiker, J. and Bickerton, W.-L., 2013. Using a Comprehensive and Standardised Cognitive Screen to Guide Cognitive Rehabilitation in Stroke. *British Journal of Occupational Therapy*, 76(3), pp. 151-156.

Blake, H., McKinney, M., Treece, K., Lee, E. and Lincoln, N.B., 2002. An evaluation of screening measures for cognitive impairment after stroke. *Age and Ageing*, (31), pp. 451-456.

Bland, J.M. and Altman, D.G., 1995. Multiple significance tests: the Bonferroni method. *BMJ*, (310), pp. 170.

Boosman, H., Winkens, I., van Heugten, C.M., Rasquin, S.M., Heijnen, V.A. and Visser-Meily, J.M., 2017. Predictors of health-related quality of life and participation after brain injury rehabilitation: The role of neuropsychological factors. *Neuropsychological Rehabilitation*, 27(4), pp. 581-598.

Bowler, J.V., 2005. Vascular cognitive impairment. *Journal of Neurology, Neurosurgery and Psychiatry*, (76), pp. 35-44.

Box, G.E.P. and Tidwell, P.W., 1962. Transformation of the independent variables. *Technometrics*, (4), pp. 531-550.

Braun, V. and Clarke, V., 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology*, 3(2), pp. 77-101.

Braun, V. and Clarke, V., 2014. *Successful qualitative research: a practical guide for beginners*. Sage: London.

Brazzelli, M., Sandercock, P.A.G., Chappell, F.M., Celani, M.G., Righetti, E., Arestis, N., Wardlaw, J.M. and Deks, J.J., 2009. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. *Cochrane Database of Systematic Reviews*, (4), doi: 10.1002/14651858.CD007424.pub2.

Brereton, L., 2002. 'Seeking': a key activity for new family carers of stroke survivors. *Journal of Clinical Nursing*, (11), pp. 22-31.

Brickman, A.M., 2013. Contemplating Alzheimer's disease and the contribution of white matter hyperintensities. *Current Neurology and Neuroscience Reports*, 13(12), doi:10.1007/s11910-013-0415-7.

British Medical Association (BMA), 2016. *Mental capacity act toolkit*. Available from: file:///C:/Users/k1811127/Downloads/Mental-capacity-act-toolkit-2016.pdf [Accessed 13th February 2019].

Broderick, J., Connolly, S., Feldmann, E., Hanley, D., Kase, C., Krieger, D., Mayberg, M., Morgenstern, L., Ogilvy, C.S., Vespa, P. and Zuccarello, M., 2007. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke*, (38), pp. 2001-23.

Brott, T., Adams, H.P., Olinger, C.P., Marler, J.R., Barsan, W.G., Biller, J., Spilker, J., Holleran, R., Eberle, R. and Hertzber, V., 1989. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*, 20(7), pp. 864-70.

Bryman, A., 1984. The Debate About Quantitative and Qualitative Research - A Question of Method or Epistemology. *British Journal of Sociology*, 35(1), pp. 75-92.

Bryman, A., 2007. Barriers to integrating quantitative and qualitative research. *Journal of Mixed Methods Research*, 1(8), pp. 8-22.

Bugge, C., Hagen, S. and Alexander, H., 2001. Measuring stroke patients' health status in the early poststroke phase using the SF36. *International Journal of Nursing Studies*, 38(3), pp. 319-327.

Bury, M., 1982. Chronic illness as biographical disruption. *Sociological of Health & Illness*, 4(2), pp. 167-182.

Bury, M., 1991. The Sociology of Chronic Illness - A Review of Research and Prospects. *Sociology of Health & Illness*, 13(4), pp. 451-468.

- Canuto, O., Ângela, M., Nogueira, L.T. and de Araújo, T.M.E., 2016. Health-related quality of life after stroke. *Acta Paulista de Enfermagem*, 29(3), pp. 245-252.
- Caplan, L.R., 1992. Intracerebral haemorrhage. *Lancet*, (339), pp. 656-658.
- Carod-Artal, F. J., Trizotto, D.S., Coral, L.F. and Moreira, C.M., 2009. Determinants of quality of life in Brazilian stroke survivors. *Journal of Neurological Sciences*, (284), pp. 63-68.
- Carod-Artal, J., Egido, J., Gonzalez, J.L. and Seijas, W., 2000. Quality of life among stroke survivors evaluated 1 year after stroke: Experience of a stroke unit. *Stroke*, (1), pp. 2995-3000.
- Carr, A.J. and Higginson, I.J., 2001. Are quality of life measures patient centred? *BMJ*, 322(7298), pp. 1357-1360.
- Carricaburu, D. and Pierret, J., 1995. From Biographical Disruption to Biographical Reinforcement - the Case of HivPositive Men. *Sociology of Health & Illness*, 17(1), pp. 65-88.
- Casebeer, A.L. and Verhoef, M.J., 1997. Combining qualitative and quantitative research methods: Considering the possibilities for enhancing the study of chronic diseases. *Chronic Diseases in Canada*, (18), pp. 130-135.
- Cassol, H., Pétré, B., Degrange, S., Martial, C., Charland-Verville, V., Lallier, F., Bragard, I., Guillaume, M. and Laureys, S., 2018. Qualitative thematic analysis of the phenomenology of near-death experiences. *PLoS ONE*, 13(2), e0193001.
- Cecil, R., Parahoo, K., Thompson, K., McCaughan, E., Power, M. and Campbell, Y., 2010. 'The hard work starts now': a glimpse into the lives of carers of community-dwelling stroke survivors. *Journal of Clinical Nursing*, (20), pp. 1723-1730.
- Chahal, N., Barker-Collo, S. and Feigin, V., 2011. Cognitive and functional outcomes of 5-year subarachnoid haemorrhage survivors: comparison to matched healthy controls. *Neuroepidemiology*, 37(1), pp. 31-38.
- Chapman, N., Huxley, R., Anderson, C., Bousser, M.G., Chalmers, J., Colman, S., Davis, S., Donnan, G., MacMahon, S., Neal, B., Warlow, C. and Woodward, M., 2004. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke

according to stroke subtype and medical history: the PROGRESS Trial. *Stroke*, 35(1), pp. 116–21.

Charidimou, A., Gang, Q. and Werring, D.J., 2012. Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum. *Journal of Neurology, Nuerosurgery and Psychiatry*, (83), pp. 124-137.

Charmaz, K., 1983. Loss of self: a fundamental form of suffering in the chronically ill. *Sociology of Health & Illness*, 5(2), pp. 168-195.

Charmaz, K., 1995. The body, identity, and self: Adapting to impairment. *Sociological Quarterly*, 36(4), pp. 657-680.

Chaves, M.L., Camozzato, A.L., Godinho, C., Kochann, R., Schuh, A., de Almeida, V.L. and Kaye, J., 2007. Validity of the clinical dementia rating scale for the detection and staging of dementia in Brazilian patients. *Alzheimer's Disease and Associated Disorders*, 21(3), pp. 210-7.

Chaudhari, T. S., Verma, R., Garg, R.K., Singh, M.K., Malhotra, H.S. and Sharma, P.K., 2014. Clinico-radiological predictors of vascular cognitive impairment (VCI) in patients with stroke: a prospective observational study. *Journal of Neurological Sciences*, (340), pp. 150-158.

Chick, N. and Meleis, A.I., 1986. Transitions: A Nursing Concern. In Chinn, P.L. (ed.) *Nursing Research Methodology*. Boulder, CO: Aspen Publication, pp 237-257.

Chien-Min, C., Tsai, C.C., Chung, C.Y., Chen, C.L., Wu, K.P. and Chen, H.C., 2015. Potential predictors for health-related quality of life in stroke patients undergoing inpatient rehabilitation. *Health & Quality of Life Outcomes*, 13(1), pp. 118-118.

Chertkow, H., Feldman, H.H., Jacova, C. and Massoud, F., 2013. Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia. *Alzheimer's Research & Therapy*, 5(1:suppl), S2.

Chou, C.Y., 2015. Determinants of the health-related quality of life for stroke survivors. *Journal of Stroke and Cerebrovascular Disorders*, 24(3), pp. 655-662.

- Christensen, M.C., Mayer, S. and Ferran, J.M., 2009. Quality of life after intracerebral haemorrhage: Results of the Factor Seven for Acute Hemorrhagic Stroke (FAST) Trial. *Stroke*, (40), pp. 1677-1682.
- Clarke, P., 2009. Understanding the experience of stroke: a mixed-method research agenda. *The Gerontologist*, 49(3), pp. 293-302.
- Clarke, P., Marshall, V., Black, S.E., Colantonio, A., 2002. Well-being after stroke in Canadian seniors: findings from the Canadian Study of Health and Aging. *Stroke*, 33(4), pp. 1016-21.
- Cohen, J., 1988. *Statistical power analysis for the behavioural sciences*. 2nd ed. New York, NY: Psychology Press.
- Connolly, A., Gaehl, E., Martin, H., Morris, J. and Purandare, N., 2011. Underdiagnosis of dementia in primary care: Variations in the observed prevalence and comparisons to the expected prevalence. *Aging & Mental Health*, 15(8), pp. 978-984.
- Corbin, J.M. and Strauss, A., 1991. A nursing model for chronic illness management based upon the Trajectory Framework. *Scholarly Inquiry for Nursing Practice*, 5(3), pp. 155-74.
- Cordonnier, C., Leys, D., Dumont, F., Deramecourt, V., Bordet, R., Pasquier, F. and Henon, H., 2010. What are the causes of pre-existing dementia in patients with intracerebral haemorrhages? *Brain*, 133(11), pp. 3281-3289.
- Corraini, P., Henderson, V.W., Ording, A.g., Pedersen, L., Horvath-Puho. And Sorensen, H.T., 2017. Long-term risk of dementia among survivors of ischemic and hemorrhagic stroke. *Stroke*, 48(1), pp. 180-186.
- Cousineau, N., McDowell, I., Hotz, S. and Hebert, P., 2003. Measuring chronic patient's feelings of being a burden to their caregivers: Development and preliminary validation of a scale. *Medical Care*, 41(1), pp. 110-118.
- Cox, D.R., 1972. Regression models and life-tables. *Journal of the Royal Statistical Society: Series B*, 34(2), pp. 187-220.
- Crawford, S., Whitnall, L., Roberston, J. and Evans, J.J., 2012. A systematic review of the accuracy and clinical utility of the Addenbrooke's Cognitive Examination and the

Addenbrooke's Cognitive Examination-Revised in the diagnosis of dementia. *International Journal of Geriatric Psychiatry*, 27(7), pp. 659-69.

Crawford, J.R., Parker, D.M. and Besson, J.A., 1988. Estimation of premorbid intelligence in organic conditions. *British Journal of Psychiatry*, (153), pp. 178-81.

Cresswell, J., 2011. Controversies in mixed methods research. In Denzin, N. and Lincoln, Y. (eds.) *The Sage Handbook of Qualitative Research*. 4th ed. London: Sage, pp. 269-283.

Creswell, J.W. and Clark, V.L.P., 2007. *Designing and Conducting Mixed Methods Research*. 1st ed. London: Sage.

Creswell, J.W. and Clark, V.L.P., 2011. *Designing and Conducting Mixed Methods Research*. 2nd ed. London: Sage.

Creswell, J.W., Clark, V.L.P., Gutmann, M. and Hanson, W., 2003. Advanced mixed methods research designs. In Tashakkori, A. and Teddlie, C. (eds.) *Handbook of Mixed Methods in Social & Behavioural Research*. Thousand Oaks, CA: Sage, pp. 209-240.

Cumming, T.B., Brodtmann, A., Darby, D. and Bernhardt, J., 2014. The importance of cognition to quality of life after stroke. *Journal of Psychosomatic Research*, 77(5), pp. 374-379.

Cumming, T.B., Marshall, R.S. and Lazar, R.M., 2013. Stroke, cognitive deficits and rehabilitation: still an incomplete picture. *International Journal of Stroke*, (8), pp. 38-45.

Delcourt, C., Zheng, D., Chen, X., Hackett, M., Arima, H., Hata, J., Heeley, E., Al-Shahi Salman, R., Woodward, M., Huang, Y., Robinson, T., Lavados, L.M., Lindley, R.I., Stapf, C., Davies, L., Chalmers, J., Anderson, C.S. and Sato, S., 2017. Associations with health-related quality of life after intracerebral haemorrhage: pooled analysis of INTERACT studies. *Journal of Neurology, Neurosurgery and Psychiatry*, (88), pp. 70-75.

Dementia Partnerships, 2012. *Dementia READ codes*. Available at: <http://dementiapartnerships.com/resource/dementia-read-codes/> [Accessed 23rd February 2015].

Dennis, M.S., 2003. Outcome after brain haemorrhage. *Cerebrovascular Diseases*, 16(1:suppl), pp. 9-13.

Dhamoon, M. S., Moon, Y.P., Paik, M.C., Boden-Albala, B., Rundek, T., Sacco, R.L. and Elkind, M.S.V., 2010. Quality of life declines after first ischemic stroke: The Northern Manhattan Study. *Neurology*, 75(4), pp. 328-334.

Dhamoon, M.S., McClure, L.A., White, C.L., Lau, H., Benavente, O. and Elkind, M.S., 2014. Quality of life after lacunar stroke: the Secondary Prevention of Small Subcortical Strokes study. *Journal of Stroke & Cerebrovascular Diseases*, 23(5), pp. 1131-1137.

Dineen, L.C. and Blakesley, B.C., 1973. Algorithm As 62: Generator for the sampling distribution of the Mann-Whitney U statistic. *Applied Statistics*, (22), pp. 269-273.

Dorman, P.J., Dennis, M. and Sandercock, P., 1999. How do scores on the EurQOL relate to scores on the SF-36 after stroke? *Stroke*, 30(10), pp. 2146-51.

Dorman, P., Slattery, J., Farrell, B., Dennis, M. and Sandercock, P., Qualitative comparison of the reliability of health status assessments with the EuroQOL and SF-36 questionnaires after stroke. United Kingdom Collaborators in the International Stroke Trial. *Stroke*, 29(1), pp. 63-8.

Dorman PJ, Waddell F, Slattery J., Dennis, M. and Sandercock, P., 1997. Are proxy assessments of health status after stroke with the EuroQOL questionnaire feasible, accurate, and unbiased? *Stroke*, (28), pp. 1883–7

Doubal, F.N., MacLulich, A.M., Ferguson, K.J., Dennis, M.S. and Wardlaw, J.M., 2010. Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. *Stroke*, (41), pp. 450–454.

Douiri, A., Rudd, A.G. and Wolfe, C.D., 2013. Prevalence of poststroke cognitive impairment: South London Stroke Register 1995-2010. *Stroke*, 44(1), pp. 138-145.

Dowswell, G., Lawler J., Dowswell T., Young, J., Forster A. and Hearn, J., 2000. Investigating recovery from stroke: a qualitative study. *Journal of Clinical Nursing*, (9), pp. 507-515.

Drotar, D., 1998. *Measuring Health-Related Quality of Life in Children and Adolescents: Implications for Research and Practice*. Mahwah, NJ: Lawrence Erlbaum Associates.

Dunn, O.J., 1964. Multiple comparisons using rank sums. *Technometrics*, (6), pp. 241-252.

Faircloth, C.A., Boylstien, C., Rittman, M. and Gubrium, J.F., 2005. Constructing the stroke: Sudden-onset narratives of stroke survivors. *Qualitative Health Research*, 15(7), pp. 928-941.

Fatoye, F. O., Komolafe, M.A., Eegunranti, B.A., Adewuya, A.O., Mosaku, S.K. and Fatoye, G.K., 2007. Cognitive impairment and quality of life among stroke survivors in Nigeria. *Psychological Reports*, (100), pp. 876-882.

Fazekas, F., Chawluk, J.B., Alavi, A., Hurtig, H.I. and Zimmerman, R.A., 1987. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *American Journal of Roentgenology Diagnostic Imaging and Related Sciences*, (149), pp. 351–356.

Feigin, V.L., Krishnamurthi, R.V., Parmar, P., Norrving, B., Mensah, G.A., Bennett, D.A., Barker-Collo, S., Moran, A.E., Sacco, R.L., Truelsen, T., Davis, S., Pandian, J.D., Naghavi, M., Forouzanfar, M.H., Nguyen, G., Johnson, C.O., Vos, T., Meretoja, A., Murray, C.J.L., Roth, G.A., GBD 2013 Writing Group, and GBD 2013 Stroke Panel Experts Group., 2015. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. *Neuroepidemiology*, (45), pp. 161-76.

Feigin, V.L., Lawes, C.M., Bennett, D.A., Barker-Collo, S.L. and Parag, V., 2009. Worldwide stroke incidence and early case fatality reported in 56 population based studies: a systematic review. *Lancet Neurology*, (8), pp. 355-69.

Ferri, C.P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., Hall, K., Hasegawa, K., Hendrie, H., Huang Y., Jorm, A., Mathers, C., Menezes, P.R., Rimmer, E., Scazufca, M. and Alzheimer's Disease International., 2005. Global prevalence of dementia: A Delphi consensus study. *Lancet*, (366), pp. 2112–2117

Fitzpatrick, R., 1999. Assessment of quality of life as an outcome: finding measurements that reflect individuals' priorities. *Quality in Health Care*, (8), pp. 102.

- Fogelholm, R., Murros, K., Rissanen, A., Avikainen, S., 2005. Long term survival after primary intracerebral haemorrhage: a retrospective population based study. *Journal of Neurology, Neurosurgery & Psychiatry*, (76), pp. 1534-1538.
- Folstein, M.F., Folstein, S.E. and McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), pp. 189-98.
- Franceschini, M., Porta, F.L., Agosti, M. and Massucci, M., 2010. Is health-related-quality of life of stroke patients influenced by neurological impairments at one year after stroke? *European Journal of Physical and Rehabilitation Medicine*, 46(3), pp. 389-399.
- Frith, H. and Gleeson, K., 2004. Clothing and embodiment: men managing body image and appearance. *Psychology of Men and Masculinity*, (5), pp. 40-48.
- Garcia, P. Y., Roussel, M., Bugnicourt, J.M., Lamy, C., Canaple, S., Peltier, J., Loas, G., Deramond, H. and Godefroy, O., 2013. Cognitive impairment and dementia after intracerebral hemorrhage: a cross-sectional study of a hospital-based series. *Journal of Stroke and Cerebrovascular Disease*, 22(1), pp. 80-86.
- Ghiso, J., Tomidokoro, Y., Revesz, T., Frangione, B. and Rostagno, A., 2011. Cerebral amyloid angiopathy and Alzheimer's disease. *Hiroaki Igaku*, 61(1:suppl), s111-124.
- Golicki, D., Niewada, M., Buczek, J., Karlinska, A., Kobayashi, A., Jannsen, M.F. and Pickard, A.S., 2015. Validity of EQ-5D-5L in stroke. *Quality of Life Research*, 24(4), pp. 845-850.
- Gorelick, P.B., Scuteri, A., Black, S.E., Decarli, C., Greenberg, S.M., Iadecola, C., Launer, L.J., Laurent, S., Lopez, O.L., Nyenhuis, D., Petersen, R.C., Schneider, J.A., Tzourio, C., Arnett, D.K., Bennett, D.A., Chui, H.C., Higashida, R.T., Lindquist, R., Nilsson, P.M., Roman, G.C., Sellke, F.W., Seshadri, S., American Heart Association Stroke Council., Council on Epidemiology and Prevention., Council on Cardiovascular Nursing., Council on Cardiovascular Radiology and Intervention and Council on Cardiovascular Surgery and Anesthesia., 2011. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American heart Association/American Stroke Association. *Stroke*, 42(9), pp. 2672-713.

Greene, J.C., Caracelli, V.J. and Graham, W.F., 1989. Toward A Conceptual Framework for Mixed-Method Evaluation Designs. *Educational Evaluation and Policy Analysis*, 11(3), pp. 255-274.

Guenther, K.M., 2009. The politics of names: rethinking the methodological and ethical significance of naming people, organizations, and places. *Qualitative Research*, (9), pp. 411-421.

Gurcay, E., Bal, A., Cakci, A., 2009. Health-related quality of life in first-ever stroke patients. *Annals of Saudi Medicine*, 29(1), pp. 36-40.

Haacke, C., Althaus, A., Spottke, A., Siebert, U., Back, T. and Dodel, R., 2006. Long-term outcome after stroke: evaluating health-related quality of life using utility measurements. *Stroke*, 37(1), pp. 193-198.

Haase, J.E. and Myers, S.T., 1988. Reconciling paradigm assumptions of qualitative and quantitative research. *Western Journal of Nursing Research*, (10), pp. 128-137.

Hachinski, V.C. and Bowler, J.V., 1993. Vascular dementia. *Neurology*, (43), pp. 2159–2160.

Hand, P.J., Wardlaw, J.M., Rowat, A.M., Haisma, J.A., Lindley, R.I. and Dennis, M.S., 2005. Magnetic resonance brain imaging in patients with acute stroke: feasibility and patient related difficulties. *Journal of Neurology, Neurosurgery and Psychiatry*, (76), pp. 1525-27.

Hart, E., 2001. System induced setbacks in stroke recovery. *Sociology of Health & Illness*, 23(1), pp. 101-123.

Hatona, S., 1976. Experience from a multicentre stroke register: a preliminary report. *Bulletin of the World Health Organisation*, (54), pp. 541-53.

Haug, T., Sorteberg, A., Finset, A., Lindegaard, K.F., Lundar, T. and Sorteberg, W., 2010. Cognitive functioning and health-related quality of life 1 year after aneurysmal subarachnoid hemorrhage in preoperative comatose patients (Hunt and Hess Grade V patients). *Neurosurgery*, 66(3), pp. 475-484.

Hemphill, J.C., Greenberg, S.M., Anderson, C.S., Becker, K., Bendok, B.R., Cushman, M., Fung, G.L., Goldstein, J.N., Macdonald, R.L., Mitchell, P.H., Scott, P.A., Selim, M.H. and

Woo, D., 2015. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*, 46(7), pp. 2032-60.

Henon, H., Durieu, I., Guerouaou, D., Lebert, F., Pasquier, F. and Leys, D., 2001. Poststroke dementia: incidence and relationship to prestroke cognitive decline. *Neurology*, 57(7), pp. 1216-1222.

Henon, H., Pasquier, F., Durieu, I., Godefroy, O., Lucas, C., Lebert, F. and Leys, D., 1997. Preexisting dementia in stroke patients. Baseline frequency, associated factors, and outcome. *Stroke*, 28(12), pp. 2429-2436.

Hilari, K., Wiggins, R.D., Roy, P., Byng, S. and Smith, S.C., 2010. Predictors of health-related quality of life (HRQL) in people with chronic aphasia. *Aphasiology*, 17(4), pp. 365-381.

Hochstenbach, J. B., Anderson, P.G., Limbeek, J.V. and Mulder, T.T., 2001. Is there a relation between neuropsychologic variables and quality of life after stroke? *Archives of Physical Medicine and Rehabilitation*, 82(10), pp. 1360-1366.

Hosmer, D.W., Lemeshow, S. and Sturdivant, R.X., 2013. *Applied logistic regression*. 3rd ed. Hoboken, NJ: Wiley.

Hounsime, N., Orrell, M. and Edwards, R.T., 2011. EQ-5D as a quality of life measure in people with dementia and their carers: evidence and key issues. *Value in Health*, 14(2), pp. 390-399.

Howe, K.R., 1988. Against the quantitative-qualitative incompatibility thesis or dogmas die hard. *Educational Researcher*, (17), pp. 10–16

Howitt, S. C., Jones, M.P., Jusabani, A., Gray, W.K., Aris, E., Mugusi, F., Swai, M. and Walker, R.W., 2011. A cross-sectional study of quality of life in incident stroke survivors in rural northern Tanzania. *Journal of Neurology*, 258(8), pp. 1422-1430.

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E. and Hodges, J.R., 2013. Validation of the Addenbrooke's Cognitive Examination III in Frontotemporal Dementia and Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders*, (36), pp. 242-250.

Huang, Y. H., Wu, C.Y., Hsieh, Y.W. and Lin, K.C., 2010. Predictors of change in quality of life after distributed constraint-induced therapy in patients with chronic stroke.

Neurorehabilitation and Neural Repair, 24(6), pp. 559-566.

Huang, Y.H., Wu, C.Y., Lin, K.C., Hsieh, Y.W., Snow, W.M. and Wang, T.N., 2013.

Determinants of Change in Stroke-Specific Quality of Life After Distributed Constraint-Induced Therapy. *American Journal of Occupational Therapy*, 67(1), pp. 54-63.

Hubbard, G. and Forbat, L., Cancer as biographical disruption: constructions of living with cancer. *Support Care Cancer*, (20), pp. 2033-2040.

Iadecola, C., Yaffe, K., Biller, J., Bratzke, L. C., Faraci, F. M., Gorelick, P. B., Gulati, M., Kamel, H., Knopman, D. S., Launer, L. J., Saczynski, J. S., Seshadri, S., Zeki Al Hazzouri, A., American Heart Association Council on Hypertension; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council, 2016. Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. *Hypertension*, 68(6), e67-e94.

Ihle-Hansen, H., Thommessen, B., Wyller, T.B., Engedal, K., Øksengård, A.R., Stenset, V., Løken, K., Aaberg, M. and Fure, B., 2011. Incidence and subtypes of MCI and dementia 1 year after first-ever stroke in patients without pre-existing cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, 32(6), pp. 401–407.

Ikram, A.M., Wieberdink, R.G. and Koudstaal, P.J., 2012. International epidemiology of intracerebral haemorrhage. *Current Atherosclerosis Reports*, (14), pp. 300-306.

Iliffe, S., 1997. Can delays in the recognition of dementia in primary care be avoided? *Aging and Mental Health*, (1), pp. 7-10.

Iliffe, S., Robinson, L., Brayne, C., Goodman, C., Rait, G., Manthorpe, J. and Ashley, P., 2009. Primary care and dementia: 1. Diagnosis, screening and disclosure. *International Journal of Geriatric Psychiatry*, 24(9), pp. 895-901.

Jackman, K.A., Cumming, T. and Miller, A.A., 2016. Chapter 11 - Stroke, Cognitive Function, and Alzheimer's Disease. In Lazorov, O. and Tesco, G. (eds.) *Genes, Environment and Alzheimer's Disease*. San Diego, CA: Academic Press, pp. 319-359.

Jacquin, A., Binquet, C., Rouaud, O., Graule-Petot, A., Daubail, B., Osseby, G.V., Bonithon-Kopp, C., Giroud, M. and Bejot, Y., 2014. Poststroke cognitive impairment: high prevalence and determining factors in a cohort of mild stroke. *Journal of Alzheimer's Disease*, 40(4), pp. 1029-1038.

Janssen, B. and Szende, A., 2014. Population Norms for the EQ-5D. In Szende, A., Janssen, B. and Cabases, J. (eds.) *Self-Reported Population Health: An International Perspective based on EQ-5D*. Dordrecht: Springer., pp. 19-30.

Jeong, B. O., Kang, H.J., Bae, K.Y., Kim, S.W., Kim, J.M., Shin, I.S., Kim, J.T., Park, M.S., Cho, K.H. and Yoon, J.S., 2012. Determinants of quality of life in the acute stage following stroke. *Psychiatry Investigation*, 9(2), pp. 127-133.

Jin, Y.P., Di Legge, S., Ostbye, T., Feightner, J.W. and Hachinski, V., 2006. The reciprocal risks of stroke and cognitive impairment in an elderly population. *Alzheimer's & Dementia*, (2), pp. 171-178.

Johnson, R.B. and Onwuegbuzie, A.J., 2004. Mixed methods research: A research paradigm whose time has come. *Educational Researcher*, (33), pp. 14-26.

Jonkman, E. J., De Weerd, A.W. and Vrijens, N.L.H., 1998. Quality of life after a first ischemic stroke long-term developments and correlations with changes in neurological deficit, mood and cognitive impairment. *Acta Neurologica Scandinavica*, 98(3), pp. 169-175.

Jonsson, A. C., Lindgren, I., Hallstrom, B., Norrving, B. and Lindgren, A., 2005. Determinants of quality of life in stroke survivors and their informal caregivers. *Stroke*, 36(4), pp. 803-808.

Jorm, A.F., 1994. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. *Psychological Medicine*, 24(1), pp. 145-53.

Karimi, M. and Brazier, J., 2016. Health, health-related quality of life and quality of life: What is the difference? *Pharmacoeconomics*, 34(7), pp. 645-649.

- Hilari, K., Wiggins, R., Roy, P., Byng, S. and Smith, S., 2010. Predictors of health-related quality of life (HRQL) in people with chronic aphasia. *Aphasiology*, 17(4), pp. 365-381.
- Kalaria, R.N., Maestre, G.E., Arizaga, R., Friedland, R.P., Galasko, D., Hall, K., Luchsinger, J.A., Ogunniyi, A., Perry, E.K., Potocnik, F., Prince, M., Stewart, R., Wimo, A., Zhang, Z-X. and Antuono, P., 2008. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurology*, 7(9), pp. 812-826.
- Kaplan, E.L. and Meier, P., 1958. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*, (53), pp. 457–81.
- Kauhanen, M. L., Korpelainen, J.T., Hiltunen, P., Nieminen, P., Sotaniemi, K.A. and Myllyla, V.V., 2000. Domains and determinants of quality of life after stroke caused by brain infarction. *Archives of Physical Medicine and Rehabilitation*, 81(12), pp. 1541-1546.
- Kelly, M.P. and Field, D., 1996. Medical sociology, chronic illness and the body. *Sociology of Health & Illness*, 18(2), pp. 241-57.
- Khan, A., Kalaria, R.N., Corbett, A. and Ballard, C., 2016. Update on vascular dementia. *Journal of Geriatric Psychiatry and Neurology*, 29(5), pp. 281-301.
- Khedr, E.M., Hamed, S.A., El-Shereef, H.K., Shawky, O.A., Mohamed, K.A., Awad, E.M., Ahmed, M.A., Shehata, G.A. and Eltahtawy, M.A., 2009. Cognitive impairment after cerebrovascular stroke: Relationship to vascular risk factors. *Neuropsychiatric Disease and Treatment*, (5), pp. 103-116.
- Kidwell, C.S. and Wintermark, M., 2008. Imaging of intracranial haemorrhage. *Lancet Neurology*, (7), pp. 256-67.
- King, R.B., 1996. Quality of life after stroke. *Stroke*, (27), pp. 1467-1472.
- Klimkowicz, A., Dziedzic, T., Slowik, A. and Szczudlik, A., 2002. Incidence of pre- and poststroke dementia: Cracow stroke registry. *Dementia and Geriatric Cognitive Disorders*, 14(3), pp. 137-140.

- Knudsen, K. A., Rosand, J., Karluk, D. and Greenberg, S.M., 2001. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Neurology*, 56(4), pp. 537-539.
- de Koning, I., van Kooten, F., Dippel, D.W., van Harskamp, F., Grobbee, D.E., Kluft, C. and Koudstaal, P.J., 1998. The CAMCOG: a useful screening instrument for dementia in stroke patients. *Stroke*, 29(10), pp. 2080-2086.
- de Koning, I., van Kooten, F., Koudstaal, P.J. and Dippel, D.W., 2005. Diagnostic value of the Rotterdam-CAMCOG in poststroke dementia. *Journal of Neurology, Neurosurgery and Psychiatry*, 76(2), pp. 263-265.
- Kreiter, K.T., Rosengart, A.J., Claassen, J., Fitzsimmons, B.F., Peery, S., Du, Y.E., Connolly, E.S., Mayer, S.A., 2013. Depressed mood and quality of life after subarachnoid hemorrhage. *Journal of the Neurological Sciences*, (335), pp. 64-71.
- Kroenke, K., Spitzer, R.L. and Williams, J.B., 2003. The patient health questionnaire-2: validity of a two-item depression screener. *Medical Care*, 41(11), pp. 1284-92.
- Kwa, V. I. H., Limburg, M. and De Haan, R.J., 1996. The role of cognitive impairment in the quality of life after ischaemic stroke. *Journal of Neurology*, 243(8), pp. 599-604.
- Kwok, T., Lo, R.S., Wong, E., Wai-Kwong, T., Mok, V. and Kai-Sing, W., 2006. Quality of life of stroke survivors: a 1-year follow-up study. *Archives of Physical Medicine and Rehabilitation*, 87(9), pp. 1177-1182.
- Laible, M., Horstmann, S., Mohlenbruch, M., Schueler, S., Rizos, T. and Veltkamp, R., 2017. Preexisting cognitive impairment in intracerebral hemorrhage. *Acta Neurologica Scandinavica*, 135(6), pp. 628-634.
- Langa, K.M. and Levine, D. A., 2015. The diagnosis and management of mild cognitive impairment: A clinical review. *JAMA*, 213(23), pp. 2551-2561.
- Larson, E. B., Kirschner, K., Bode, R.K., Heinemann, A.W., Clorfene, J. and Goodman, R., 2003. Brief cognitive assessment and prediction of functional outcome in stroke. *Topics in Stroke Rehabilitation*, 9(4), pp. 10-21.

Lawrence, M., 2010. Young adults' experience of stroke: a qualitative review of the literature. *British Journal of Nursing*, 19(4), pp. 241-8.

Lee, A. C. K., Tang, S.W., Tsoi, T.H., Fong, D.Y.T. and Yu, G.K.K., 2009. Predictors of poststroke quality of life in older Chinese adults. *Journal of Advanced Nursing*, 65(3), pp. 554-564.

Lefebvre, C., Deplanque, D., Touze, E., Henon, H., Parnetti, L., Pasquier, F., Gallai, V. and Leys, D., 2005. Prestroke dementia in patients with atrial fibrillation: frequency and associated factors. *Journal of Neurology*, 252(12), pp. 1504-1509.

Lincoln, Y.S. and Guba, E.G., 1985. *Naturalistic Inquiry*. Newbury Park, CA: Sage Publications.

Lloyd, V., Gatherer, A. and Kalsy, S., 2006. Conducting Qualitative Interview Research with People with Expressive Language Difficulties. *Qualitative Health Research*, (16), pp. 1386-1401.

Locock, L., Ziebland, S. and Dumelow, C., 2009. Biographical disruption, abruption and repair in the context of motor neurone disease. *Sociology of Health & Illness*, 31(7), pp. 1043-1058.

Lopez, O.L., Becker, J.T., Klunk, W., Saxton, J., Hamilton, R.L., Kaufer, D.I., Sweet, R.A., Meltzer, C., Wisniewski, S., Kamboh, M.I. and DeKosky, S.T., 2000. Research evaluation and diagnosis of probable Alzheimer's disease over the last two decades: I. *Neurology*, 55(12), pp. 1854-62.

Lovelock, C.E., Anslow, P., Molyneux, A.J., Byrne, J.V., Kuker, W., Pretorius, P.M., Coull, A. and Rothwell, P.M., 2009. Substantial Observer Variability in the Differentiation Between Primary Intracerebral Hemorrhage and Hemorrhagic Transformation of Infarction on CT Brain Imaging. *Stroke*, (40), pp. 3763-67.

Lovelock, C.E., Molyneux, A.J. and Rothwell, P.M., 2007. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurology*, (6), pp. 487-93.

Lyden, P., Lu, M., Jackson, P., Marler, J., Kothari, R., Brott, T. and Zivin, J., 1999. Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. *Stroke*, 30(11), pp. 2347-54.

Lyons, R., Rudd, A. and Alvaro, C., 2007. Advances in health policy. *Stroke*, 39(2), pp. 264-267.

Madureira, S., Guerreiro, M. and Ferro, J.M., 2001. Dementia and cognitive impairment three months after stroke. *European Journal of Neurology*, 8(6), pp. 621-627.

de Man-van, G.J.M., Gooskens, F., Schepers, V.P., Schuurmans, M.J., Lindeman, E. Hafsteinsdottir, T.B., 2012. Screening for poststroke depression using the patient health questionnaire. *Nursing Research*, 61(5), pp. 333-41.

Mayer, S. A., Kreiter, K.T., Copeland, D., Bernardini, G.L., Bates, J.E., Peery, S., Claassen, J., Du, Y.E. and Connolly Jr, E.S., 2002. Global and domain-specific cognitive impairment and outcome after subarachnoid hemorrhage. *Neurology*, 59(11), pp. 1750-1758.

McCulla, M.M., Coats, M., Van Fleet, N., Duchek, J., Grant, E., Morris, J.C., 1989. Reliability of clinical nurse specialists in the staging of dementia. *Archives of Neurology*, (46), pp. 1210–1211.

McPherson, C., Wilson, K. and Murray, M., 2007. Feeling like a burden: Exploring the perspectives of patients at the end of life. *Social Science & Medicine*, (64), pp. 417-427.

McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R. Jr, Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S. and Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimers & Dementia*, 7(3), pp. 263–269.

Menard, S., 1995. *Applied logistic regression analysis. Sage University Paper Series on Quantitative Applications in the Social Sciences*. Thousand Oaks, CA: Sage.

Meyer, B., Ringel, F., Winter, Y., Spottke, A., Gharevi, N., Dams, J., Balzer-Geldsetzer, M., Mueller, I.K., Klockgether, T., Schramm, J., Urbach, H. and Dodel, R., 2010. Health-related

quality of life in patients with subarachnoid haemorrhage. *Cerebrovascular Diseases*, 30(4), pp. 423-431.

Mitchell, A.J. Kemp, S. Benito-Leon, J. and Reuber, M., 2010. The influence of cognitive impairment on health-related quality of life in neurological disease. *Acta Neuropsychiatrica*, (22), pp. 2-13.

Morgan, D.L., 1998. Practical strategies for combining qualitative and quantitative methods: applications to health research. *Qualitative Health Research*, (8), pp. 362-376.

Morris, J.C., 1993. The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology*, (43), pp. 2412–2414

Morris, R., 2011. The psychology of stroke in young adults: the roles of service provision and return to work. *Stroke Research and Treatment*, (2011), doi:10.4061/2011/534812.

Morse, J., Barrett, M., Mayan, M., Olson, K. and Spiers, J., 2002. Verification strategies for establishing reliability validity in qualitative research. *International Journal of Qualitative Research*, (1), pp. 1-19.

Moulin, S., Labreuche, J., Bombois, S., Rossi, C., Boulouis, G., Henon, H., Duhamel, A., Leys, D. and Cordonnier, C., 2016. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. *Lancet Neurology*, 15(8), pp. 820-829.

Mead, G., Lynch, J., Greig, C., Young, A., Lewis, S. and Sharpe, M., 2007. Evaluation of fatigue stroke scales in stroke patients. *Stroke*, 38(7), pp. 2090-5.

Medical Research Council (MRC), 2000. *A framework for the development and evaluation of RCTs for complex interventions to improve health*. MRC: London.

Murao, K., Rossi, C. and Cordonnier, C., 2013. Intracerebral haemorrhage and cognitive decline. *Revue Neurologique*, 169(10), pp. 772-778.

Myers, R., 1990. *Classical and modern regression with applications*. 2nd ed. Boston, MA: Duxbury.

National Institute for Health and Care Excellence (NICE), 2006. *Dementia: Supporting People With Dementia And Their Carers In Health And Social Care*. Available from: <https://www.nice.org.uk/Guidance/Cg42> [Accessed 22nd March 2016].

Nelson, H. E., 1982. *National Adult Reading Test (NART): For the assessment of premorbid intelligence in patients with dementia: Test manual*. NFER-Nelson: Windsor.

Nelson, H.E. and O'Connell, A., 1978. Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex*, 14(2), pp. 234-44.

Newman, G.C., 2007. Clarification of abc/2 rule for ICH volume. *Stroke*, 38(3), pp. 862.

Noble, A. J., Baisch, S., Mendelow, A.D., Allen, L., Kane, P. and Schenk, T., 2008. Posttraumatic stress disorder explains reduced quality of life in subarachnoid hemorrhage patients in both the short and long term. *Neurosurgery*, 63(6), pp. 1095-1104.

Noble, H. and Smith, J., 2015. Issues of validity and reliability in qualitative research. *Evidence Based Nursing*, 18(2), pp. 34-35.

Nys, G. M. S., van Zandvoort, M.J.E., van der Worp, H.B., de Haan, E.H.F., de Kort, P.L.M., Jansen, B.P.W. and Kappelle, L.J., 2006. Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke. *Journal of the Neurological Sciences*, 247(2), pp. 149-156.

Nys, G. M., van Zandvoort, M.J., de Kort, P.L., Jansen, B.P., de Haan, E.H. and Kappelle, L.J., 2007. Cognitive disorders in acute stroke: prevalence and clinical determinants. *Cerebrovascular Diseases*, 23(5-6), pp. 408-416.

O'Brien, J.T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., Bowler, J.V., Ballard, C., DeCarli, D., Gorelick, P.B., Rockwood, K., Burns, A., Gauthier, S. and DeKosky, S.T., 2003. Vascular cognitive impairment. *Lancet Neurology*, (2), pp. 89-98.

O'Carroll, R.E. and Gilleard, C.J., 1986. Estimation of premorbid intelligence in dementia. *British Journal of Clinical Psychology*, 25(2), pp. 157-158.

Pantoni, L., 2010. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurology*, (9), pp. 689-701.

- Palinkas, L.A., Horwitz, S.M., Green, C.A., Wisdom, J.P., Duan, N. and Hiawood, K., 2015. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Administration and Policy in Mental Health and Mental Health*, 42(5), pp. 533-544.
- Pantoni, L., 2010. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurology*, (9), pp. 689–701
- Park, J. H., Kim, B.J., Bae, H.J., Lee, J., Lee, J., Han, M.K., O, K.Y., Park, S.H., Kang, Y., Yu, K.H. and Lee, B.C., 2013. Impact of poststroke cognitive impairment with no dementia on health-related quality of life. *Journal of Stroke*, 15(1), pp. 49-56.
- Passier, P. E., Visser-Meily, J.M., van Zandvoort, M.J., Rinkel, G.J., Lindeman, E. and Post, M.W., 2012. Predictors of long-term health-related quality of life in patients with aneurysmal subarachnoid hemorrhage. *NeuroRehabilitation*, 30(2), pp. 137-145.
- Patel, M. D., Coshall, C., Rudd, A.G. and Wolfe, C.D., 2002. Cognitive impairment after stroke: clinical determinants and its associations with long-term stroke outcomes. *Journal of the American Geriatrics Society*, 50(4), pp. 700-706.
- Patel, M. D., McKeivitt, C., Lawrence, E., Rudd, A.G. and Wolfe, C.D.A., 2007. Clinical determinants of long-term quality of life after stroke. *Age and Ageing*, 36(3), pp. 316-322.
- Patton, M.Q., 2002. *Qualitative research and evaluation methods*. 3rd ed. Thousand Oaks, CA: Sage Publications.
- Peixoto, B., Silva, S., Carreira, S., Sousa, D., Rezende, V. and Teixeira, A., 2017. Quality of life predictors after first stroke: A study with post-acute patients. *Neurology Psychiatry and Brain Research*, (23), pp. 10-15.
- Pendlebury, S.T. and Rothwell, P.M., 2009. Prevalence, incidence, and factors associated with prestroke and poststroke dementia: a systematic review and meta-analysis. *Lancet Neurology*, 8(11), pp. 1006-18.
- Pendlebury, S.T., Mariz, J., Bull, L., Mehta, Z. and Rothwell, P.M., 2012. MoCA, ACE-R, and MMSE Versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke

Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery After TIA and Stroke. *Stroke*, (43), pp. 464-469.

Pendlebury, S. T., Chen, P., Bull, L., Silver, L., Mehta, Z., & Rothwell, P. M., 2015. Methodological factors in determining rates of dementia in TIA and stroke (I): impact of baseline selection bias. *Stroke*, 46(3), pp. 641–646.

Petersen, R.C., 2011. Mild Cognitive Impairment. *New England Journal of Medicine*, 364, pp. 2227-2234.

Planton, M., Raposo, N., Danet, L., Albucher, J.F., Peran, P. and Pariente, J., 2017 (a). Impact of spontaneous intracerebral hemorrhage on cognitive functioning: An update. *Revue Neurologique*, 173(7-8), pp. 481-489.

Planton, M., Siant-Aubert, L., Raposo, N., Branchu, L., Lyoubi, A., Bonneville, F., Albucher, J.F., Olivot, J.M., Peran, P. and Parient, J., 2017 (b). High prevalence of cognitive impairment after intracerebral haemorrhage. *PLoS ONE*, 12(6), e0178886.

Pollock, A., St George, B., Fenton, M. and Firkins, L., 2012. Top ten research priorities relating to life after stroke. *Lancet Neurology*, 11(3), pp.209.

Pollock, A. and Berge, E., 2018. How to do a systematic review. *International Journal of Stroke*, 13(2), pp. 138-156.

Poon, M.T., Fonville, A.F. and Al-Shahi Salman, R., 2014. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *Journal of Neurology Neurosurgery and Psychiatry*, 85(6), pp. 660-7.

Pound, P., Gompertz, P and Ebrahim, S., 1998. A patient-centred study of the consequences of stroke. *Clinical Rehabilitation*, (12), 338-347.

Prince, M., Knapp, M., Guerchet, M., McCrone, P., Prina, M., Comas-Herrers, M., Wittenverg, A., Adelais, R., Hu, B., King, B., Rehill, D. and Salimkumar, D., 2014. *Dementia UK: Second Edition*. Alzheimer's Society: London.

- Qu, Y., Zhuo, L., Li, N., Hu, Y., Chen, W., Zhou, Y., Wang, J., Tao, Q., Hu, J., Nie, X. and Zhan, S., 2015. Prevalence of poststroke cognitive impairment in china: a community-based, cross-sectional study. *PLoS One*, 10(4), e0122864.
- Querfurth, H.W. and LaFerla, F.M., 2010. Alzheimer's disease. *The New England Journal of Medicine*, (362), pp. 329–344
- Qureshi, A.I., Mendelow, A.D. and Hanley, D.F., 2009. Intracerebral haemorrhage. *Lancet*, 373(9675), pp. 1632-1644.
- Rachpukdee, S., Howteerakul, N., Suwannapong, N. and Tang-Aroonsin, S., 2013. Quality of life of stroke survivors: a 3-month follow-up study. *Journal of Stroke and Cerebrovascular Diseases*, 22(7), e70-78.
- Ramsay, P., 2010. *Quality of life following prolonged critical illness: A mixed methods study*. PhD Thesis. University of Edinburgh. Available from: <https://www.era.lib.ed.ac.uk/bitstream/handle/1842/8310/Ramsay%20PhD%202010.pdf?sequence=1&isAllowed=y> [Accessed 6th February 2019].
- Rikkert, M.G., Tona, K.D., Janssen, L., Burns, A., Lobo, A., Robert, P., Sartorius, N., Stoppe, G. and Waldemar, G., 2011. Validity, reliability, and feasibility of clinical staging scales in dementia: a systematic review. *American Journal of Alzheimer's Disease and Other Dementias*, 26(5), pp. 357-65.
- Rincon, C.G., 2013. Studying outcomes that matter to patients and families: quality of life after intracerebral haemorrhage. *American Journal of Respiratory and Critical Care Medicine*, (188), pp. 1278-9.
- Rittman, M., Faircloth, C., Boylstien, C., Gubrium, J.F., Williams, C., van Puymbroeck, M. and Ellis, C., 2004. The experience of time in the transition from hospital to homes following stroke. *Journal of Rehabilitation Research and Development*, 41(3), pp. 259-68.
- Rodrigues, M.A., Samarasekera, N., Lerpiniere, C., Humphreys, C., McCarron, M.O., White, P.M., Nicoll, J.A.R., Sudlow, C.L.M., Cordonnier, C., Wardlaw, J.M., Smith, C. and Al-Shahi Salman, R., 2018. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral

haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. *The Lancet Neurology*, 17(3), pp. 232-240.

Roman, G.C., Tatemichi, T.K., Erkinjuntti, T., Cummings, J.L., Masfeu, J.C., Garcia, J.H., Amaducci, L., Orgogozo, J.M., Brun, A., Hofman, A., Moody, D.M., O'Brien, M.D., Yamaguchi, T., Grafman, J., Drayer, B.P., Bennett, D.A., Fisher, M., Ogato, J., Kokmen, E., Bermejo, F., Wolf, P.A., Gorelick, P.B., Bick, K.L., Pajean, A.K., Bell, M.A., DeCarli, C., Culebras, A., Korczyn, A.D., Bogousslavsky, J., Hartmann, A. and Scheinberg, P., 1993. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*, (43), pp. 250-260.

Rost, N. S., Smith, E.E., Chang, Y., Snider, R.W., Chanderraj, R., Schwab, K., FitzMaurice, E., Wendell, L., Goldstein, J.N., Greenberg, S.M. and Rosand, J., 2008. Prediction of functional outcome in patients with primary intracerebral hemorrhage: the FUNC score. *Stroke*, 39(8), pp. 2304-2309.

Russell, C., 1999. Interviewing vulnerable old people: ethical and methodological implications of imaging our subjects. *Journal of Aging Studies*, (13), pp. 403-417.

Russell, M.W., Boulanger, L., Joshi, A.V., Neumann, P.J. and Menzin, J., 2006. The economic burden of intracerebral hemorrhage: evidence from managed care. *Managed Care Interface*, 19(6), pp. 24-28.

Safaz, I, Serdar K, Emre A, and Bilge Y., 2016. Determinants of disease-specific health-related quality of life in Turkish stroke survivors. *International Journal of Rehabilitation Research*, 39(2), pp. 130-133.

Samarasekera, N., Fonville, A., Lerpiniere, C., Farrall, A.J., Wardlaw, J.M., White, P.M., Smith, C., Al-Shahi Salman, R. and the Lothian Audit of the Treatment of Cerebral Haemorrhage (LATCH) collaborators., 2015. Influence of intracerebral haemorrhage location on incidence, characteristics and outcome: a population-based study. *Stroke*, (46), pp. 361-8.

Samarasekera, N., Smith, C. and Al-Shahi Salman, R., 2012. The association between cerebral amyloid angiopathy and intracerebral haemorrhage: systematic review and meta-analysis. *Journal of Neurology, Neurosurgery and Psychiatry*, (83), pp. 275-81.

Sanders, C., Donovan, J. and Dieppe, P., 2002. The significance and consequences of having painful and disabled joints in older age: co-existing accounts of normal and disrupted biographies. *Sociology of Health & Illness*, 24(2), pp. 227-253.

Sarfo, F.S., Akassi, J., Adamu, S., Obese, V. and Ovbiagele, B., 2017. Burden and Predictors of Poststroke Cognitive Impairment in a Sample of Ghanaian Stroke Survivors. *Journal of Stroke and Cerebrovascular Diseases*, 26(11), pp. 2553-2562.

Sato, S., Delcourt, C., Heeley, E., Arima, H., Zhang, S., Al-Shahi Salman, R., Stapf, C., Woo, D., Flaherty, M.L., Vagal, A., Levi, C., Davies, L., Wang, J., Robinson, T., Lavados, P.M., Lindley, R.I., Chalmers, J., Anderson, C.S. and INTERACT2 investigators, 2016. Significance of Cerebral Small-Vessel Disease in Acute Intracerebral Hemorrhage. *Stroke*, 47(3), pp. 701-7.

Savage, I.R., 1956. Contributions to the theory of rank order statistics: The two sample case. *Annals Mathematical Statistics*, 27(3), pp. 590–615.

Scott, R. B., Eccles, F., Lloyd, A. and Carpenter, K., 2008. From multidimensional neuropsychological outcomes to a cognitive complication rate: the International Subarachnoid Aneurysm Trial. *Trials*, 9(13), doi: 10.1186/1745-6215-9-13.

Shannon-Baker, P., 2015. Making paradigms meaningful in mixed methods research. *Journal of Mixed Methods Research*, 10(4), pp. 319-334.

Scrambler, G., 2009. Health-related stigma. *Sociology of health & Illness*, 31(3), pp. 441-455.

Smith, E.E. and Eichler, F., 2006. Cerebral amyloid angiopathy and lobar intracerebral hemorrhage. *Archives of Neurology*, (63), pp. 148-51

Smith, E. E., Gurol, M.E., Eng, J.A., Engel, C.R., Nguyen, T.N., Rosand, J. and Greenberg, S.M., 2004. White matter lesions, cognition, and recurrent hemorrhage in lobar intracerebral hemorrhage. *Neurology*, 63(9), pp. 1606-1612.

Smith, E.E. and Venegas-Torres, J.A., 2014. Cognitive dysfunction after intracerebral haemorrhage, vasculitis, and other stroke syndromes. In Schweizer, T.A. and Macdonald, R.L. (eds.) *The behavioural consequences of stroke*. New York, NY: Springer, pp. 199-226.

- Smith, L.N., Lawrence, M., Kerr, S.M., Langhorne, P. and Lees, K.R., 2003. Informal carers' experience of caring for stroke survivors. *Journal of Advanced Nursing*, 46(3), pp. 235-244.
- Spieth, L.E. and Harris, C.V., 1996. Assessment of health-related quality of life in children and adolescents: An integrative review. *Journal of Paediatric Psychology*, (21), pp. 175-193.
- Springer, M. V., Schmidt, J.M., Wartenberg, K.E., Frontera, J.A., Badjatia, N. and Mayer, S.A., 2009. Predictors of global cognitive impairment 1 year after subarachnoid hemorrhage. *Neurosurgery*, 65(6), pp. 1043-1050.
- Staals, J., Makin, S.D., Doubal, F.N., Dennis, M.S. and Wardlaw, J.M., 2014. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*, 83(14), pp. 1228-1234.
- Steiner, T., Al-Shahi Salman, R., Beer, R., Christensen, H., Cordonnier, C., Csiba, L., Forsting, M., Harnof, S., Klijn, C.J., Krieger, D., Mendelow, A.D., Molina, C., Montaner, J., Overgaard, K., Petersson, J., Roine, R.O., Schmutzhard, E., Schwerdtfeger, K., Stapf, C., Tatlisumak, T., Thomas, B.M., Toni, D., Unterberg, A. and Wagner, M., 2014. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral haemorrhage. *International Journal of Stroke*, 9(7), pp. 840–855.
- Stolwyk, R.J., O'Neill, M.H., McKay, A.J. and Wong, D.K., 2014. Are screening tools sensitive and specific enough for use after stroke? A systematic literature review. *Stroke*, 45(10), pp. 3129-34.
- Stroke Association, 2012. *Struggling to recover: life after stroke campaign briefing*. Available from: https://www.stroke.org.uk/sites/default/files/struggling_to_recover_report_lowres.pdf [Accessed 2nd march 2019].
- Sturm, J.W., Donnan, G.A., Dewey, H.M., Macdonell, R.A.L., Gilligan, A.K., Srikanth, V. and Thrift, A.G., 2004. Quality of life after stroke: The North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke*, (35), pp. 2340-2345.

- van Swieten, J.C., Hijdra, A., Koudstaal, P.J. and van Gijn, J., 1990. Grading white matter lesions on CT and MRI: a simple scale. *Journal of Neurology Neurosurgery and Psychiatry*, 53(12), pp. 1080-3.
- van Swieten, J.C., Koudstaal, P.J., Visser, M.C., Schouten, H.J. and van Gijn, J., 1988. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, (19), pp. 604-07.
- Takemasa, S., Nakagoshi, R., Uesugi, M., Inoue, Y., Gotou, M., Koeda, H. and Naruse, S., 2016. Factors affecting the quality of life of homebound elderly hemiparetic stroke patients with cognitive impairment. *Journal of Physical Therapy Science*, 28(12), pp. 3376-3379.
- Tang, W. K., Chan, S.S., Chiu, H.F., Ungvari, G.S., Wong, K.S., Kwok, T.C., Mok, V., Wong, K.T., Richards, P.S. and Ahuja, A.T., 2004. Frequency and determinants of poststroke dementia in Chinese. *Stroke*, 35(4), pp. 930-935.
- Tang, W. K., Chan, S.S., Chiu, H.F., Ungvari, G.S., Wong, K.S., Kwok, T.C., Mok, V., Wong, K.T., Richards, P.S. and Ahuja, A.T., 2006. Frequency and clinical determinants of poststroke cognitive impairment in nondemented stroke patients. *Journal of Geriatric Psychiatry and Neurology*, 19(2), pp. 65-71.
- Tashakkori, A. and Teddlie, C., 2010. *Handbook of mixed methods in social and behavioural research*. 2nd ed. Thousand Oaks, CA: Sage.
- Tashakkori, A. and Teddlie, C., 1998. *Mixed methodology: Combining qualitative and quantitative approaches*. Thousand Oaks, CA: Sage.
- Taufique, Z., May, T., Meyers, E., Falo, C., Mayer, S.A., Agarwal, S., Park, S., Connolly, E.S., Claassen, J. and Schmidt, J.M., 2016. Predictors of Poor Quality of Life 1 Year After Subarachnoid Hemorrhage. *Neurosurgery*, 78(2), pp. 256-264.
- Thal, D.R., Grinberg, L.T. and Attems, J., 2012. Vascular dementia: different forms of vessel disorders contribute to the development of dementia in the elderly brain. *Experimental Gerontology*, (47), pp. 816-24.

Tjahjadi, M., Heinen, C., Konig, R., Rockels, E., Wirtz, C.R., Woischneck, D. and Kapapa, T., 2013. Health-related quality of life after spontaneous subarachnoid hemorrhage measured in a recent patient population. *World Neurosurgery*, 79(2), pp. 296-307.

Tong, A., Sainsbury, P. and Craig, J., 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*, 19(6), pp. 349 – 357

Torrance, G.W., 1987. Utility approach to ensuring health-related quality of life. *Journal of Chronic Diseases*, 40(6), pp. 593-600.

Turner, A., Hambridge, J., White, J., Carter, G., Clover, K., Nelson, L. and Hackett, M., 2012. Depression screening in stroke: A Comparison of Alternative Measures With the Structured Diagnostic Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Major Depressive Episode) as Criterion Standard. *Stroke*, 43(4), pp. 1000-1005.

Tveiten, A., Ljostad, U., Mygland, A. and Naess, H., 2014. Functioning of long-term survivors of first-ever intracerebral hemorrhage. *Acta Neurologica Scandinavica*, 129(4), pp. 269-275.

Varona, J.F., Bermejo, F., Guerra, J.M. and Molina, J.A., 2004. Long-term prognosis of ischemic stroke in young adults. Study of 272 cases. *Journal of Neurology*, 251(12), pp. 1507-14.

Verhoeven, C.L.M., Post, M.W.M., Schiemanck, S.K., van Zandvoort, M.J.E., Vrancken, P.H. and van Heugten, C.M., 2011a. Is cognitive functioning 1 year poststroke related to quality of life domain? *Journal of Stroke and Cerebrovascular Diseases*, 20(5), pp. 450-458.

Verhoeven, C.L.M, Schepers, V.P., Post, M.W.M. and van Heugten, C.M., 2011b. The predictive value of cognitive impairments measured at the start of clinical rehabilitation for health status 1 year and 3 years poststroke. *International Journal of Rehabilitation Research*, 34(1), pp. 38-43.

Vilkkki, J., Juvela, S., Malmivaara, K., Siironen, J. and Hernesniemi, J., 2012. Predictors of work status and quality of life 9-13 years after aneurysmal subarachnoid hemorrhage. *Acta Neurochirurgica*, 154(8), pp. 1437-1446.

Viswanathan, A. and Greenberg, S.M., 2011. Cerebral amyloid angiopathy in the elderly. *Annals of Neurology*, (70), pp. 871-880.

Viswanathan, A., Patel, P., Rahman, R., Nandigam, R.N., Kinnecom, C., Bracoud, L., Rosand, J., Chabriat, H., Greenberg, S.M. and Smith, E.E., 2008. Tissue microstructural changes are independently associated with cognitive impairment in cerebral amyloid angiopathy. *Stroke*, 39(7), pp. 1988-1992.

Wardlaw, J.M., Smith, C. and Dichgans, M., 2013. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurology*, (12), pp. 483-97.

Ware, J.E., Snow, K.K., Kosinski, M. and Gandek, B., 1993. *SF-36 health survey: manual and interpretation guide*. Boston, MA: The Health Institute, New England Medical Centre.

Warlow, C., van Gijn, J., Dennis, M., Wardlaw, J., Bamford, J.M., Hankey, G., Sandercock, P.A., Rinkel, G.J.E., Langhorne, P., Sudlow, C. and Rothwell, P., 2008. *Stroke: Practical Management*. 3rd ed. Edinburgh: Blackwell Publishing.

Warlow, C., Sudlow, C., Dennis, M., Wardlaw, J. and Sandercock, P., 2003. Stroke. *Lancet*, (362), pp. 1211-24.

Webb, A.J.S., Pendlebury, S.T., Li, L., Simoni, M., Lovett, N., Mehta, Z. and Rothwell, P.M., 2014. Validation of the Montreal Cognitive Assessment versus Mini-Mental State Examination against hypertension and hypertensive arteriopathy after Transient Ischemic Attack or Minor Stroke. *Stroke*, 45(11), pp. 3337-42.

WHOQOL Group, 1998. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychological Medicine*, (28), pp. 551-558.

van Wijk, I., Gorter, J.W., Lindeman, E., Kappelle, L.J., van Gijn, J., Koudstaal, P.J. and Algra, A., 2007. Mental status and health-related quality of life in an elderly population 15 years after limited cerebral ischaemia. *Journal of Neurology*, 254(8), pp. 1018-1025.

Williams, G., 1984. The genesis of chronic illness: narrative re-construction. *Sociology of Health & Illness*, 6(2), pp. 175-200.

Williams, S. J., 2000. Chronic illness as biographical disruption or biographical disruption as chronic illness? Reflections on a core concept. *Sociology of Health & Illness*, 22(1), pp. 40-67.

Williams, L.S., Brizendine, E.J., Plue, L., Bakas, T., Tu, W., Hendrie, H. and Kroenke, K., 2005. Performance of the PHQ-9 as a screening tool for depression after stroke. *Stroke*, 36(3), pp. 635-8.

Wolfenden, B. and Grace, M., 2015. Vulnerability and poststroke experiences of working-age survivors during recovery. *SAGE Open*, (2015), pp. 1-14.

Woo, D., Sauerbeck, L.R., Kissela, B.M., Khoury, J.C., Szaflarski, J.P., Gebel, J., Shukla, R., Panciolo, A.M., Jauch, E.C., Menon, A.G., Deka, R., Carrozzella, J.A., Moomaw, C.J., Fontaine, R.N. and Broderick, J.P., 2002. Genetic and environmental risk factors for intracerebral haemorrhage: preliminary results of a population-based study. *Stroke*, (33), pp. 1190-1196.

World Health Organization (WHO), 2014. *Constitution of the World Health Organization*. 48th ed. Geneva: World Health Organization.

Wu, A.W., Jacobson, D.L., Frick, K.D., Clark, R., Revicki, D.A., Freedberg, K.A., Scott-Lennox, J. and Feinberg, J., 2002. Validity and responsiveness of the EuroQOL as a measure of health-related quality of life in people enrolled in an AIDS clinical trial. *Quality of Life Research*, (11), pp. 273-282.

Xiong, L., Reijmer, Y.D., Chardimou, A., Cordonnier, C. and Viswanathan, A., 2016. Intracerebral haemorrhage and cognitive impairment. *Biochimica et Biophysica Acta*, 1862(5), pp. 939-44.

Yim, E., Sekar, P., Moomaw, C., Osbrone, J., Martini, S., Xiong, L., Biffi, A., Rosand, J. and Woo, D., 2018. Impact of pre-existing dementia on intracerebral haemorrhage outcomes. *Neurology*, 90(15:suppl), S10.008.

van Zandvoort, M. J., Kessels, R.P., Nys, G.M., de Haan, E.H. and Kappelle, L.J., 2005. Early neuropsychological evaluation in patients with ischaemic stroke provides valid information. *Clinical Neurology and Neurosurgery*, 107(5), pp. 385-392.

Zhang, Y., Zhang, Z., Yang, B., Li, Y., Zhang, Q., Qu,, Q., Wang, Y., Zhang, S., Yue, W., Tan, Y., Zhang, B. and Xu, T., 2012. Incidence and risk factors of cognitive impairment 3 months after first-ever stroke: a cross-sectional study of 5 geographic areas of China. *Journal of Huazhong University of Science and Technology (Medical Sciences)*, 32(6), pp. 906-911.

Zulkifly, M. F., Ghazali, S. E., Che Din, N., Singh, D. K. and Subramaniam, P., 2016. A Review of Risk Factors for Cognitive Impairment in Stroke Survivors. *The Scientific World Journal*, (2016), doi:10.1155/2016/3456943.

Appendices

Appendix 1: PRISMA checklist

Appendix 2: STROBE checklist

Appendix 3: STROBE quality assessment scores for studies of intracerebral haemorrhage and cognitive decline

Appendix 4: STROBE quality assessment scores for studies of the influence of cognitive impairment on health-related quality of life after stroke

Appendix 5: LINCHPIN COG Research Ethics Committee approval

Appendix 6: Research & Development approval- LINCHPIN COG

Appendix 7: LINCHPIN COG consent form

Appendix 8: LINCHPIN COG patient information sheet

Appendix 9: LINCHPIN COG participant assessments

Appendix 10: LINCHPIN COG participant feedback letter (template)

Appendix 11: Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Appendix 12: Interview Schedule

Appendix 13: 15-Point Checklist of Criteria for Good Thematic Analysis Process

Appendix 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	

Appendix 2: STROBE checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Appendix 3: STROBE quality assessment scores for studies of intracerebral haemorrhage and cognitive decline

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total
<i>Altieri et al, 2004</i>	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	19
<i>Arauz et al, 2014</i>	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	21
<i>Banjeree et al, 2018</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Barba et al, 2000</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	20
<i>Barba et al, 2001</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	20
<i>Bejot et al, 2011</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Benedictus et al, 2015</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Biffi et al, 2016</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Chaudhari et al, 2014</i>	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	19
<i>Cordonnier et al, 2010</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>De Koning et al, 1998</i>	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	21
<i>De Koning et al, 2005</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Douiri, Rudd and Wolfe, 2013</i>	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	21
<i>Garcia et al, 2013</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	21
<i>Henon et al, 1997</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	21
<i>Henon et al, 2001</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Ihle-Hansen et al, 2011</i>	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	1	18

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total
<i>Khedr et al, 2009</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	20
<i>Jacquín et al, 2014</i>	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	20
<i>Klimkowitz et al, 2002</i>	1	0	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	1	0	0	14
<i>Laible et al, 2017</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	21
<i>Lefebvre et al, 2005</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Madureira et al, 2001</i>	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	20
<i>Moulin et al, 2016</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Nys et al, 2007</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Patel et al, 2002</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Planton et al, 2017b</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Qu et al, 2015</i>	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	20
<i>Rost et al, 2008</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	21
<i>Smith et al, 2004</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	20
<i>Tang et al, 2004</i>	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	20
<i>Tang et al, 2006</i>	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	20
<i>Tveiten et al, 2014</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Viswanathan et al, 2008</i>	1	1	1	1	1	1	1	1	0	0	1	1	0	1	1	1	1	1	1	1	0	1	18
<i>Zhang et al, 2012</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22

Appendix 4: STROBE quality assessment scores for studies of the influence of cognitive impairment on health-related quality of life after stroke

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total
<i>Adamit et al, 2015</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Alvarez-Sabin et al, 2016</i>	1	1	1	0	1	1	1	0	1	0	1	1	0	1	1	1	1	1	1	1	0	0	16
<i>Ankolekar et al, 2014</i>	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	21
<i>Barker-Collo et al, 2010</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Boosman et al, 2017</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	21
<i>Bugge et al, 2001</i>	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	19
<i>Canuto et al, 2016</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	20
<i>Carod-Artal et al, 2009</i>	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	20
<i>Chahal et al, 2011</i>	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	21
<i>Chen-Min et al, 2015</i>	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	20
<i>Chou et al, 2015</i>	0	1	1	1	1	0	1	1	1	0	1	1	0	1	1	1	1	1	0	1	0	0	15
<i>Clarke et al, 2002</i>	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	21
<i>Cumming et al, 2014</i>	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	21
<i>Dhamoon et al, 2010</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	20
<i>Dhamoon et al, 2014</i>	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	19
<i>Fatoye et al, 2007</i>	1	1	1	1	0	0	1	1	0	0	1	1	0	1	1	1	1	1	0	1	1	0	15

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total
<i>Franceschini et al, 2010</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	20
<i>Gurcay et al, 2009</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	20
<i>Haacke et al, 2006</i>	0	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	18
<i>Haug et al, 2010</i>	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	17
<i>Hilari et al, 2010</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	21
<i>Hochstenbach et al, 2002</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Howitt et al, 2011</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Huang et al, 2010</i>	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	20
<i>Huang et al, 2013</i>	0	1	1	1	0	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	18
<i>Jeong et al, 2012</i>	0	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	19
<i>Jonkman et al, 1998</i>	0	1	0	1	0	0	1	1	1	0	1	0	0	0	1	1	1	1	1	1	0	1	13
<i>Jonsson et al, 2005</i>	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	20
<i>Karmel et al, 2010</i>	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0	0	18
<i>Kauhanen et al, 2000</i>	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	20
<i>Kwa et al, 1996</i>	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	19
<i>Kwok et al, 2006</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Larson et al, 2003</i>	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	19
<i>Lee et al, 2009</i>	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	21

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total
<i>Mayer et al, 2002</i>	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	21
<i>Meyer et al, 2010</i>	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	19
<i>Noble et al, 2008</i>	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	19
<i>Nys, G.M.S 2005</i>	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	20
<i>Park et al, 2013</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Passier et al, 2012</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	21
<i>Patel et al, 2007</i>	1	1	1	1	1	1	0	0	1	1	0	1	1	1	1	1	1	1	1	1	0	0	17
<i>Peixoto et al, 2017</i>	0	1	1	1	0	1	1	1	1	0	0	1	0	1	1	1	1	1	1	1	0	0	15
<i>Rachpukde et al, 2013</i>	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	19
<i>Safaz et al, 2016</i>	0	1	1	1	0	1	1	1	0	0	1	1	0	1	1	1	1	1	1	1	0	0	15
<i>Sarfo et al, 2017</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	21
<i>Scott et al, 2008</i>	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	19
<i>Springer et al, 2009</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Takemasa et al, 2016</i>	0	1	1	1	0	0	1	1	0	0	1	1	0	0	0	1	0	1	0	1	0	0	10
<i>Taufique et al, 2016</i>	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	20
<i>Van Wijk et al, 2007</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
<i>Verhoeven et al, 2011a</i>	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	0	19
<i>Verhoeven et al, 2011b</i>	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	20

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total
<i>Vilkki et al, 2012</i>	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	19
<i>Van Zandvoort et al, 2005</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22

Appendix 5: LINCHPIN COG Research Ethics Committee approval

Scotland A Research Ethics Committee

Research Ethics Service
Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Direct Telephone: 0131
465 5678
Dorothy.Garrow@nhslothian.scot.nhs.uk
Dorothy.Garrow@nhs.net



06 March 2015

Dr Rustam Al-Shahi Salman
University of Edinburgh
Bramwell Dott Building
Western General Hospital
Edinburgh
EH4 2XU

Dear Dr Al-Shahi-Salman

Study title:	Lothian study of INtraCerebral Haemorrhage Pathology, Imaging and Neurological outcome (LINCHPIN)
REC reference:	10/MRE00/23
EudraCT number:	n/a
Amendment number:	REC Reference AM05
Amendment date:	13 February 2015
IRAS project ID:	36344

The above amendment was reviewed at the meeting of the Sub-Committee held in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Chairman Dr Ian Zealley
Vice-Chairman Dr Colin Selley

Approved documents

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering letter on headed paper		16 February 2015
GP/consultant information sheets or letters [LINCHPIN COG summary letter for GP/participant]	1.0	18 December 2014
Non-validated questionnaire [LINCHPIN COG questionnaires for those with mental capacity]	1.0	18 December 2014
Non-validated questionnaire [LINCHPIN COG questionnaires for those without mental capacity]	1.0	18 December 2014
Notice of Substantial Amendment (non-CTIMP)		13 February 2015
Other [Addendum 1 (LINCHPIN COG protocol)]	1.0	09 January 2015
Other [LINCHPIN COG feedback options]	1.0	09 January 2015
Other [SOP for patient with mental capacity]	1.0	16 December 2014
Participant consent form [LINCHPIN COG consent form for those with mental capacity]	1.0	08 October 2014
Participant consent form [LINCHPIN COG consent form for those without mental capacity]	1.0	08 October 2014
Participant information sheet (PIS) [LINCHPIN COG patient information sheet for those with mental capacity]	1.0	09 January 2015
Participant information sheet (PIS) [LINCHPIN COG patient information sheet for those without mental capacity]	1.0	09 January 2015
Research protocol or project proposal	5.0	20 November 2014

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

10/MRE00/23:	<i>Please quote this number on all correspondence</i>
---------------------	--

Yours sincerely

A handwritten signature in black ink, appearing to read 'Colin Selby'.

Dr Colin Selby
Chair

Copy to: *Dr Rustam Al-Shahi Salman, University of Edinburgh*

Appendix 6: Research & Development approval- LINCHPIN COG

University Hospitals Division

Queen's Medical Research Institute
47 Little France Crescent, Edinburgh, EH16 4TJ



SS/NM

12 March 2015

Dr Neshika Samarasekera
University of Edinburgh
Division of Clinical Neurosciences
Bramwell Dott Building, Western General Hospital
Crewe Road
Edinburgh
EH4 2XU

RESEARCH & DEVELOPMENT
Room E1.12
Tel: 0131 242 3330
Email:
R&DOffice@nhslothian.scot.nhs.uk

Director:
Professor David E Newby

Dear Dr Samarasekera

REC No:	10/MRE00/23
R&D Project ID No:	2010/W/NEU/04
Amendment:	Substantial amendment No.4 dated 20 January 2015
Title of Research	LINCHPIN: Lothian study of INtraCerebral Haemorrhage Pathology, Imaging and Neurological outcome

I am writing in reply to recent correspondence in relation to an amendment(s) to the above project and the subsequent updated documents as follows.

- o Addendum 1 - COG Protocol version 1 dated 09 January 2015
- o COG Consent Form (Capacity) version 1 dated 08 October 2014
- o COG Consent Form (Without Capacity) version 1 dated 08 October 2014
- o COG Feedback Summary version 1 dated 09 January 2015
- o COG Patient Information Sheet (Capacity) version 1 dated 09 January 2015
- o COG Patient Information Sheet (without Capacity) version 1 dated 09 January 2015
- o COG Questionnaire (With Capacity) version 1 dated 18 December 2014
- o COG Questionnaire (Without Capacity) version 1 dated 18 December 2014
- o COG Summary Letter version 1 dated 18 December 2014
- o SOP Consent for Mental Capacity version 1 dated 16 December 2014
- o Protocol (Clean and tracked) version 5 dated 20 November 2014
- o End of study extension to 31 January 2017

We have now assessed any consequential changes and can confirm that NHS Lothian management approval is extended to cover the specific changes intimated.

Yours sincerely

A handwritten signature in cursive script that reads 'Susan Shepherd'.

Mrs Susan Shepherd
Head of Research Governance

cc: Professor Rustam Al-Shahi Salman, Chief Investigator, WGH

Appendix 7: LINCHPIN COG consent form

Lothian study of INtraCerebral Haemorrhage Pathology, Imaging and Neurological outcome COGnition sub-study (LINCHPIN COG):



Consent form for participants with mental capacity

Name of researcher: Katie McGoochan

LINCHPIN ID:

Please
initial box

1. I confirm that I have read the information sheet dated..... (version.....) for the above sub-study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected.
3. I agree to being contacted in about 6 months for a follow-up appointment.
4. I agree to my GP being contacted with the results of the additional assessment.
5. I would / would not * like to receive feedback on the results of my assessment. (*delete as appropriate)
6. I would / would not * like to receive information about the results of the research. (*delete as appropriate)
7. I agree to take part in the above sub-study.

☐☐☐☐☐☐☐

Name of participant

Date

Signature

Name of person taking
consent

Date

Signature



**Lothian study of IntraCerebral Haemorrhage
Pathology, Imaging and Neurological
outcome COGnition sub-study
(LINCHPIN COG)**



Participant information sheet

Thank you for taking part in the LINCHPIN study. We would now like to invite you to take part in an extension of LINCHPIN, called LINCHPIN COG. The aim of this sub-study is to look at how stroke due to bleeding into the brain (known as 'brain haemorrhage') affects mental abilities such as thinking, knowing and remembering.

Joining LINCHPIN COG is entirely up to you. Before you decide we would like you to understand why this additional research is being done and what it would involve for you. Please feel free to talk to others about the sub-study if you wish.

Part 1 of the Participant Information Sheet tells you the purpose of the additional assessments and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the sub-study.

Part 1

What is the purpose of the sub-study?

About 1 in every 5 strokes are caused by brain haemorrhage. Around 15,000 people in the UK will have a bleed like this every year and the effects can be very serious.

LINCHPIN COG aims to assess what impact a brain haemorrhage has on your mental ability, health and daily life.

Gaining a greater understanding of the impact of this type of stroke could help identify strategies to help with the long-term consequences of brain haemorrhage.

Why have I been asked to take part?

We are asking you to take part because you have had a brain haemorrhage and have already consented to all or part of LINCHPIN. We are giving you the opportunity to participate in this sub-study because it may help us to understand more about the impact that a brain haemorrhage can have on your health and life.

Do I have to take part?

It is up to you. If you agree to take part, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This will not affect the care you receive or your participation in LINCHPIN.

What will happen to me if I take part?

1. Clinical Assessment

As part of this sub-study, we ask that you attend a 60 minute appointment with a member of our team. At the appointment, the researcher will work through a number of questionnaires. These

questionnaires will be used to assess your mental ability, physical function, mood and overall health and wellbeing.

If you are attending the follow-up clinic at the Anne Rowling Centre as part of LINCHPIN, it may be possible to combine the two sessions in order to save you further trips. If it is more convenient, the researcher can come to your home at a time that is suitable for you.

2. Checking how you get on in the future

We would like to check how you are getting on at a follow-up appointment in six months. This can either be held at the Anne Rowling Clinic or the researcher can come to your home if this is more convenient.

There may also be a further opportunity to speak with the researcher one-to-one about your experiences of having a stroke and how it has impacted upon your daily life.

If the information in **Part 1** has interested you and you are considering taking part, please read the additional information in **Part 2** before making any decision.

Part 2

Will my taking part be kept confidential?

Yes. Your identity is totally confidential and no identifying details will ever be made public.

How will information about me be handled?

LINCHPIN COG is run by a team from the Centre for Clinical Brain Sciences in Edinburgh. The information is processed by this team, which includes medical, computing and administrative staff. All members have NHS contracts and a professional duty of confidentiality. The information is held securely in a password protected database. All identifying information is removed before the data are analysed. We comply with the Data Protection Act, 1998.

Will I get the results of the assessment?

The researcher will be more than happy to give you feedback on the assessments that you complete.

What are the potential disadvantages?

Apart from the time taken in order to carry out the questionnaires, there are no disadvantages of this assessment.

What happens when the research study stops?

Information about you will be retained indefinitely.

Will my GP be informed about my participation?

Yes. Your GP will be informed of the results of the additional assessments.

If I agree now, can I change my mind later?

Yes. Do contact us if you need to discuss anything (see back page).

What if there is a problem?

If you have a concern about any aspect of this study, you should speak to one of the research team who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this via the NHS Complaints Procedure, whose details can be obtained from the hospital.

Can I find out the results of the research?

We would be very happy to send you a yearly newsletter about the results of the research, if you wish. The results of the sub-study will be submitted for publication in relevant professional journals and also made available in a format appropriate to the general public. When the results are published, we will not include any individual information about you that would be identifiable.

Who is funding this research?

LINCHPIN COG is funded by The Stroke Association.

Who has reviewed the study?

The Scotland A Research Ethics Committee approved this study.

Thank you for reading this information leaflet.

Independent advice about this study is available from:

Professor M Dennis, Chair of Stroke Medicine, Centre for Clinical Brain Sciences, The University of Edinburgh, The Chancellor's Building, Little France, Edinburgh, EH16 4SB.

Telephone: 0131 465 9602 Email: martin.dennis@ed.ac.uk

If you would like further information please contact one of the research team:

Katie McGoohan (LINCHPIN COG researcher)

Prof. Rustam Al-Shahi Salman (chief investigator of LINCHPIN)

Telephone: 0131 537 2944

Email: s0804748@sms.ed.ac.uk

Appendix 9: LINCHPIN COG participant assessments

LINCHPIN COG Study – Patient demographics and medical history

Participant Identification Number:
Date:

Social Details					
Education	Primary	Secondary	Further	Higher/Graduate	Other
Occupation	Manual		Non-manual		Other
Lives alone	Yes			No	
Pre-ICH residency	Own Home	Residential Home	Nursing Home	Hospital	Other
Current residency	Own Home	Residential Home	Nursing Home	Hospital	Other
Smoker	Never	Current	Ex	Unknown	
Alcohol Consumption (Units/Week):	0	1-7	8-14	15-21	>21
Medical History					
Stroke severity (questions asked at onset):			Able to talk? Yes/No/Unknown Orientated to time, place and person? Yes/No/Unknown Able to lift both arms? Yes/No/Unknown Can walk unaided? Yes/No/Unknown		
Pre-morbid Rankin Scale score (0-5):					
Significant co-morbidities occurring before and after the index ICH:			Ischemic stroke or TIA? Yes/No/Unknown Recurrent ICH? Yes/No/Unknown Hypertension? Yes/No/Unknown Depression? Yes/No/Unknown Diabetes mellitus? Yes/No/Unknown Myocardial infarction? Yes/No/Unknown Angina? Yes/No/Unknown Atrial Fibrillation? Yes/No/Unknown		
History of dementia:			Yes/No/Unknown If yes, what type?		
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE):			Completed? Yes/No		

Under each heading, please tick the **ONE** box that best describes your health
TODAY

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

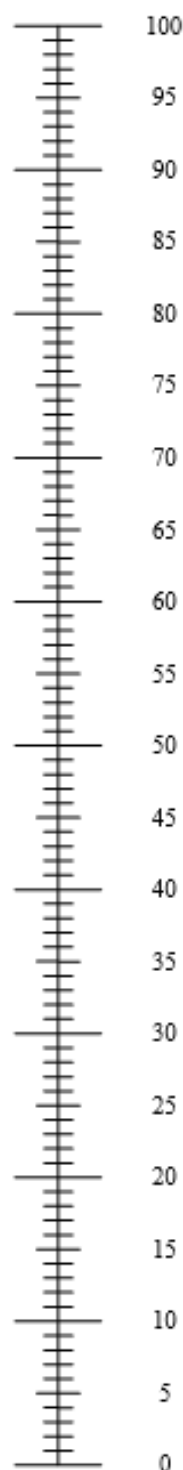
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

CLINICAL DEMENTIA RATING (CDR)					
	0	0.5	1	2	3
	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented to place of examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgement & Problem Solving	Solves everyday problems and handles business and financial affairs well; judgement good in relation to past performances	Slight impairment in solving problems, similarities and differences	Moderate difficulty in handling problems, similarities and differences; social judgement usually maintained	Severely impaired in handling problems, similarities and differences; social judgement usually impaired	Unable to make judgements or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretence of independent function outside home Appears well enough to be taken to functions outside the family home; independent function	Appears too ill to be taken to functions outside the family home
Home & Hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home, hobbies and intellectual interest slightly impaired	Mild but definite impairment of function at home more difficult tasks abandoned; more complicated hobbies and interests abandoned	Only simple tasks preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Full capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Over the last two weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite: being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

SF-36 vitality scale

These questions are about how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time in the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Did you have a lot of energy?	1	2	3	4	5
Did you feel full of life?	1	2	3	4	5
Did you feel worn out?	1	2	3	4	5
Did you feel tired?	1	2	3	4	5

National Adult Reading Test

CHORD	<input type="checkbox"/>	SUPERFLUOUS	<input type="checkbox"/>
ACHE	<input type="checkbox"/>	SIMILE	<input type="checkbox"/>
DEPOT	<input type="checkbox"/>	BANAL	<input type="checkbox"/>
AISLE	<input type="checkbox"/>	QUADRUPED	<input type="checkbox"/>
BOUQUET	<input type="checkbox"/>	CELLIST	<input type="checkbox"/>
PSALM	<input type="checkbox"/>	FAÇADE	<input type="checkbox"/>
CAPON	<input type="checkbox"/>	ZEALOT	<input type="checkbox"/>
DENY	<input type="checkbox"/>	DRACHM	<input type="checkbox"/>
NAUSEA	<input type="checkbox"/>	AEON	<input type="checkbox"/>
DEBT	<input type="checkbox"/>	PLACEBO	<input type="checkbox"/>
COURTEOUS	<input type="checkbox"/>	ABSTEMIOUS	<input type="checkbox"/>
RAREFY	<input type="checkbox"/>	DÉTENTE	<input type="checkbox"/>
EQUIVOCAL	<input type="checkbox"/>	IDYLL	<input type="checkbox"/>
NAIVE	<input type="checkbox"/>	PUERPERAL	<input type="checkbox"/>
CATACOMB	<input type="checkbox"/>	AVER	<input type="checkbox"/>
GAOLED	<input type="checkbox"/>	GAUCHE	<input type="checkbox"/>
THYME	<input type="checkbox"/>	TOPIARY	<input type="checkbox"/>
HEIR	<input type="checkbox"/>	LEVIATHAN	<input type="checkbox"/>
RADIX	<input type="checkbox"/>	BEATIFY	<input type="checkbox"/>
ASSIGNATE	<input type="checkbox"/>	PRELATE	<input type="checkbox"/>
HIATUS	<input type="checkbox"/>	SIDEREAL	<input type="checkbox"/>
SUBTLE	<input type="checkbox"/>	DEMESNE	<input type="checkbox"/>
PROCRATE	<input type="checkbox"/>	SYNCOPE	<input type="checkbox"/>
GIST	<input type="checkbox"/>	LABILE	<input type="checkbox"/>
GOUGE	<input type="checkbox"/>	CAMPANILE	<input type="checkbox"/>

Cognitive Questions

	<u>Participant Response</u>	<u>Score</u>
ORIENTATION TO TIME		
What is the... year?	_____	0 1
season?	_____	0 1
month of the year?	_____	0 1
day of the week?	_____	0 1
date?	_____	0 1

ORIENTATION TO PLACE

Where are you now? What is the...		
country (or region)?	_____	0 1
county (or city/town)?	_____	0 1
city/town (or district)?	_____	0 1
building (name or type)?	_____	0 1
floor of the building	_____	0 1

REGISTRATION

Listen carefully. I am going to say three words. You say them back after I stop. Ready?
 Here they are... LEMON [pause], KEY [pause], BALL [pause]. Now repeat those words back to me.
 [Repeat up to 5 times, but score only the first trial.]

LEMON	_____	0 1
KEY	_____	0 1
BALL	_____	0 1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

ATTENTION AND CALCULATION [Serial 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop. If participant makes a mistake, do not stop. Let the participant carry on and check subsequent answers.

What is 100 take away 7? [93]	_____	0 1
If needed, say: Keep going. [86]	_____	0 1
If needed, say: Keep going. [79]	_____	0 1
If needed, say: Keep going. [72]	_____	0 1
If needed, say: Keep going. [65]	_____	0 1

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.

Spell WORLD forwards, then backwards.

Correct forward spelling if misspelled, but score only the backward spelling.

(D = 1) (L = 1) (R = 1) (O = 1) (W = 1)	(0 to 5)
---	----------

RECALL

What were those three words I asked you to remember? *[Do not offer any hints.]*

LEMON	_____	0	1
KEY	_____	0	1
BALL	_____	0	1

NAMING

What is this? *[Point to a pencil or pen.]*

_____ 0 1

What is this? *[Point to a watch.]*

_____ 0 1

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.

[Repeat up to 5 times, but score only the first trial.]

NO IFS, ANDS, OR BUTS. 0 1

COMPREHENSION

Listen carefully because I am going to ask you to do something.

Take this paper in your right hand *[pause]*, **fold it in half** *[pause]*, **and put it on the floor** *(or table)*.

TAKE IN RIGHT HAND _____ 0 1

FOLD IN HALF _____ 0 1

PUT ON FLOOR (or TABLE) _____ 0 1

READING

Please read this and do what it says. *[Show participant the words from the participant pack.]*

CLOSE YOUR EYES _____ 0 1

DRAWING

Please copy this design. *[Display the intersecting pentagons from the participant pack.]*

Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. 0 1

ANIMALS

Now can you name as many animals as possible. It can begin with any letter.

_____ (0 to 7)

Score 0= <5 Score 1= 5-6 Score 2= 7-8 Score 3= 9-10 Score 4= 11-13 Score 5= 14-16 Score 6= 17-21 Score 7= >21.

MEMORY

I'm going to give you a name and address and I'd like you to repeat them after me. So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later.

	1 st Trial	2 nd Trail	3 rd Trial	
Harry Barnes	_____	_____	_____	0 1 2
73 Orchard Close	_____	_____	_____	0 1 2 3
Kingsbridge	_____	_____	_____	0 1
Devon	_____	_____	_____	0 1

MEMORY

What is the...

Name of current Prime Minister?	_____	0	1
Name of the woman who was Prime Minister?	_____	0	1
Name of the USA president?	_____	0	1
Name of the USA president who was assassinated in the 1960's?	_____	0	1

LANGUAGE

Place a pencil and piece of paper in front of the participant. As a practice trial, ask the participant to "Pick up the pencil and then the paper." If incorrect, score 0 and do not continue further.

If the participant is correct on the practice trial, continue by asking the following:

Place the paper on top of the pencil.	_____	0	1
Pick up the pencil but not the paper.	_____	0	1
Pass me the pencil after touching the paper.	_____	0	1

Note: Place the pencil and paper in front of the subject before each command.

WRITING

Please write two sentences. It can be about anything you like.

0 1 2

If the participant does not know what to write about, you could suggest a few topics.

Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil.

Score 1 point for each if the sentence is comprehensible and contains a subject and a verb.

Ignore errors in grammar or spelling.

LANGUAGE

Ask the participant to repeat:

'caterpillar'; 'eccentricity'; 'unintelligible'; 'statistician'

0 1 2

Score 2 if all correct; score 1 if 3 are correct; and score 0 if 2 or less are correct.

Ask the participant to repeat:

'All that glitters is not gold'

0 1

'A stitch in time saves nine'

0 1

LANGUAGE- Naming:

Ask the participant to **name the objects in the participant pack**:

(0 to 13)

LANGUAGE- Comprehension:

Using the pictures above, ask the participant to:

Point to the one which is associated with the monarchy

0 1

Point to the one which is a marsupial

0 1

Point to the one which is found in the Antarctic

0 1

Point to the one which has a nautical connection

0 1

LANGUAGE- Reading:

Ask the participant to read the following words:

0 1

sew

pint

soot

dough

height

DRAWING

Please copy this diagram. [*Display the infinity diagram from the participant pack.*]

0 1

DRAWING

Please copy this drawing. [*Display the wire cube from the participant pack.*]

0 1

DRAWING

Ask the participant to **draw a clock face with numbers.**

Then, ask the participant to **put the hands at ten past five.**

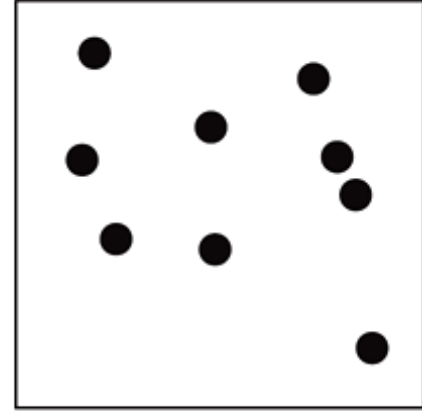
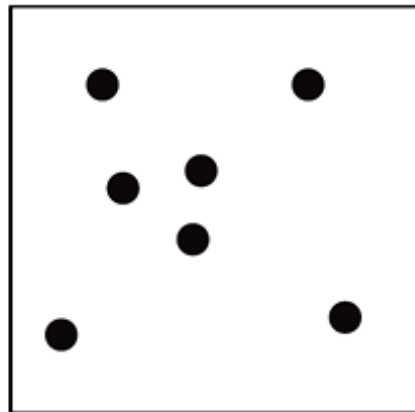
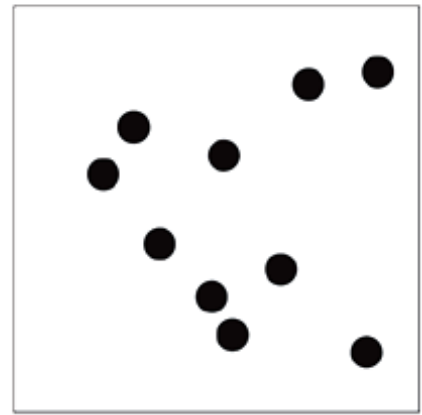
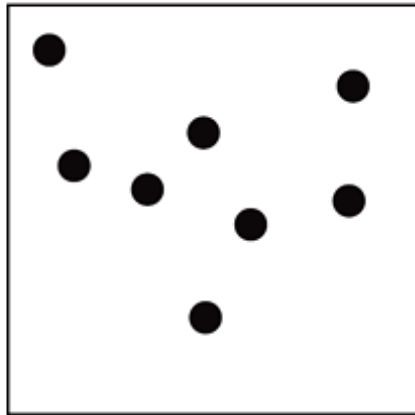
(0 to 5)

[Circle = 1, numbers = 2, hands = 2 if all correct]

VISIOSPATIAL ABILITIES

Ask the participant to **count the dots without pointing to them.**

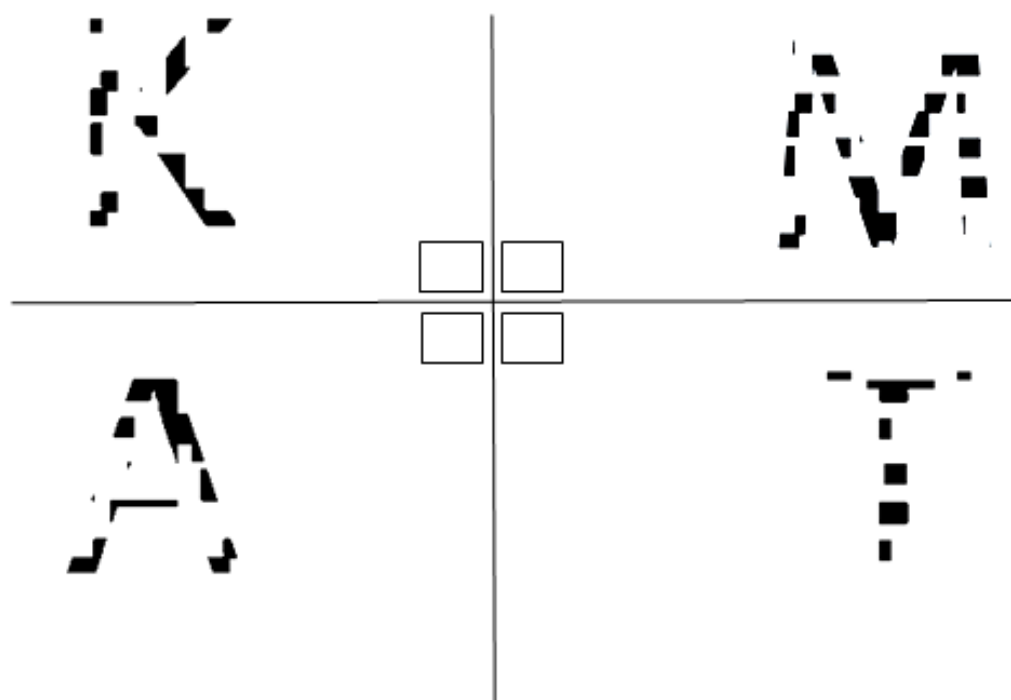
(0 to 4)



VISIOSPATIAL ABILITIES

Ask the participant to **identify the letters**.

(0 to 4)



MEMORY

Ask 'Now tell me what you remember of that name and address we were repeating earlier on' _____

(0 to 7)

Harry	Barnes	73	Orchard	Close	Kingsbridge	Devon

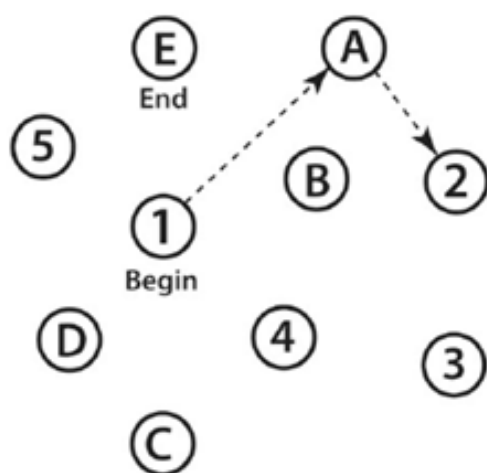
This test should be done if the participant failed to recall one or more items above. If all items were recalled, skip this part and score 5. If only part was recalled, start by ticking items recalled in the shadowed column on the right hand side and then test not recalled items by giving multiple choice options. Each recognised item scores 1 point, which is added to the points gained by recalling.

(0 to 5)

Jerry Barnes		Harry Barnes		Harry Bradford		recalled	
37		73		76		recalled	
Orchard Place		Oak Close		Orchard Close		recalled	
Oakhampton		Kingsbridge		Dartington		recalled	
Devon		Dorset		Somerset		recalled	

EXECUTIVE

0 1



MEMORY

I'm going to give you five words and I'd like you to repeat them after me.

After participant repeats, say **Try to remember them because I'm going to ask you later.**

Do 2 trials, even if 1st is successful. Do a recall after 5 minutes. Do not score.

	FACE	VELVET	CHURCH	DAISY	RED
1 st Trail					
2 nd Trail					

ATTENTION

Read list of digits (1 digit/sec).

Participant to **repeat in forward order**: 2 1 8 5 4 _____ 0 1

Participant to **repeat in the backward order**: 7 4 2 _____ 0 1

Read list of letters. The participant must **tap with their hand at each letter A**. 0 1

No points if 2 or more errors.

F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

LANGUAGE

Ask the participant to repeat:

I only know that John is the one to help today	0	1
The cat always hid under the couch when dogs were in the room	0	1

FLUENCY

I'm going to give you a letter of the alphabet and I would like you to generate as many words as you can beginning with that letter, but not names of people or places. For example, If the letter was "C", you could give me words like "cat, cry and clock" and so on. But you can't give me words like "Catherine or Canada".

Do you understand? Are you ready? You have one minute. The letter I want you to use is "P".

ACE-III: Score 0= 0-1 Score 1= 2-3 Score 2= 4-5 Score 3= 6-7 Score 4= 8-10 Score 5= 11-13 Score 6= 14-17 Score 7= >17.

MoCA: Score 1 if 11 or more words identified.

--

ABSTRACTION

Ask the participant to **name the similarity between the following words**. For example, the similarity between a banana and an orange = fruit.

Train – bicycle	_____	0	1
Watch – ruler	_____	0	1

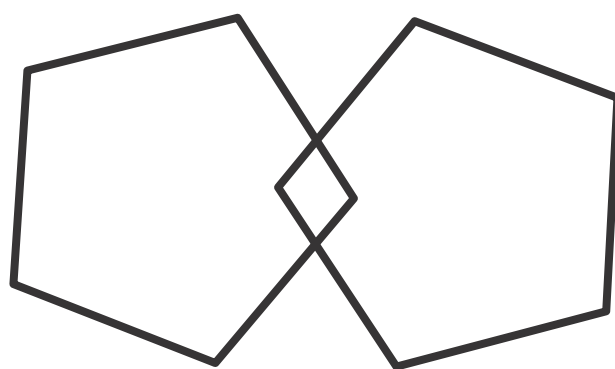
DELAYED RECALL

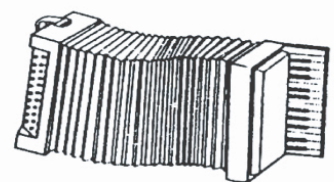
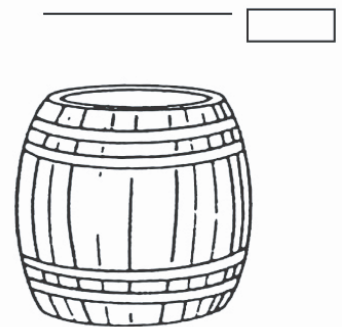
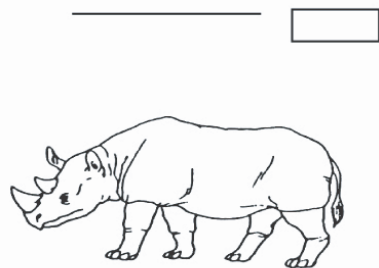
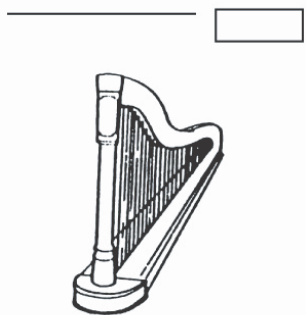
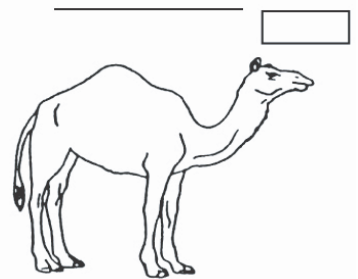
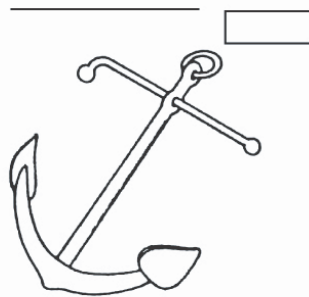
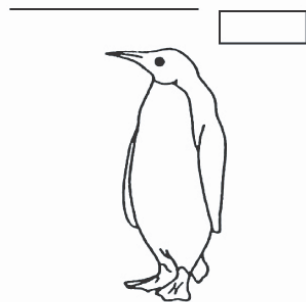
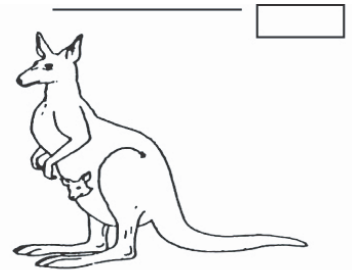
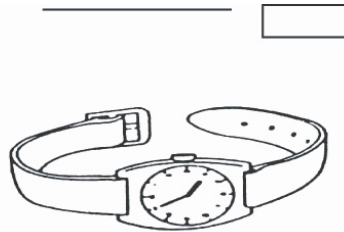
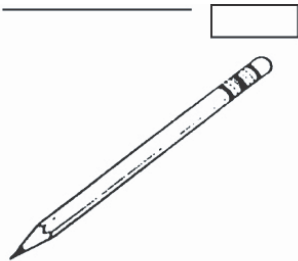
Ask participant to recall the words from earlier with no cue:

_____ (0 to 5)

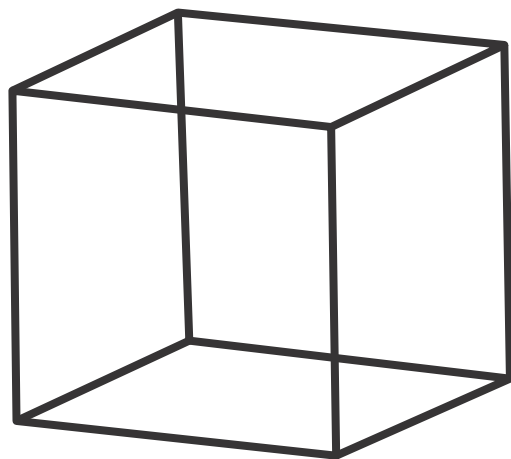
FACE	VELVET	CHURCH	DAISY	RED

CLOSE YOUR EYES









Appendix 10: LINCHPIN COG participant feedback letter (template)

Version 1: 18/12/2014



<Patient name>
<Patient address>

CENTRE FOR CLINICAL BRAIN SCIENCES
The University of Edinburgh
First Floor
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49 Little France Crescent
Edinburgh, EH16 4SB

Project Coordinator (Rosemary Anderson): +44 (0)131 537 2944
Email: s0804748@sms.ed.ac.uk

04 April 2019

Dear <Patient title> <Patient surname>

Many thanks for participating in the LINCHPIN COG sub-study.
Please find a brief summary of your results on the next page.

If you have any further questions about the sub-study or any of the
assessments or your results, please contact Katie McGoochan at
s0804748@sms.ed.ac.uk or 0131 537 2944.

Yours sincerely

Rustam Al-Shahi Salman

Katie McGoochan
Nurse Researcher
NMC No. 0911086S

Rustam Al-Shahi Salman
*Professor of clinical neurology
and honorary consultant neurologist*
GMC No. 4067993

cc. general practitioner

CENTRE DIRECTOR: Professor S Chandran
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SENIOR CLINICAL FELLOWS: Professor R Al-Shahi Salman (MRC), Dr A Williams (CSO), Dr D Mahad (CSO)
CLINICIAN SCIENTISTS: Dr W Whiteley (MRC), Dr D Hunt (Wellcome)

The University of Edinburgh is a charitable body, registered in Scotland, with registration number SC005336.

Your test results in the LINCHPIN COG sub-study

What we tested	Your score	What your score means
<i>Mood</i>		
Patient Health Questionnaire-9		
<i>Fatigue</i>		
SF-36 vitality scale		
<i>Stroke Severity</i>		
National Institutes of Health Stroke Scale		
<i>Cognition</i>		
Addenbrooke's Cognitive Examination-III		
Mini Mental State Examination		
Montreal Cognitive Assessment		
<i>Physical function</i>		
Timed Get Up and Go		

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Appendix 11: Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

(Tong, Sainsbury and Craig 2007)

No. Item	Guide questions/description	Notes
Domain 1: Research team and reflexivity		
<i>Personal Characteristics</i>		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	KMcG
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Bachelor of Nursing (Hons) and Master of Nursing in Clinical Research
3. Occupation	What was their occupation at the time of the study?	Postgraduate Nurse Researcher
4. Gender	Was the researcher male or female?	Female
5. Experience and training	What experience or training did the researcher have?	Clinical and research experience with stroke patients
<i>Relationship with participants</i>		
6. Relationship established	Was a relationship established prior to study commencement?	No relationship was established prior to commencement of LIICHPIN COG. However, prior to the qualitative interviews, participants would have met with the researcher on at least two previous occasions (clinic and MRI visits)
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Participants were informed that the research was to fulfill the requirements for a PhD in Nursing Studies and to further understanding of patient and family experiences of life after stroke due to haemorrhage. Participants were informed that their participation would not affect the standard of care they received

8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	The interviewer (KMcG) was a nurse and member of the LINCHPIN research team, but not a member of the participants' direct clinical team. To reduce the risk of researcher bias, the interview schedule was created with the support of the researcher's academic and clinical supervisors and the patient representative group. In addition, the researcher's supervisor provided alternative viewpoints to the researchers throughout several phases of the thematic analysis
Domain 2: Study design		
<i>Theoretical framework</i>		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Thematic analysis Inductive (data-driven) Pragmatism
<i>Participant selection</i>		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Purposeful
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Face-to-face
12. Sample size	How many participants were in the study?	6 patients and 4 family members
13. Non-participation	How many people refused to participate or dropped out? Reasons?	None
<i>Setting</i>		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Participants were given a choice between a clinic setting or their home for the interviews. All opted for their home

15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Four of the participants requested that their partners be present during the interview
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Participants are introduced in section 10.8
<i>Data collection</i>		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Semi-structured interview schedule provided in Appendix 2, developed in collaboration with academic and clinical supervisors, as well as the patient representative group
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	None
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Audio recorded using encrypted software
20. Field notes	Were field notes made during and/or after the inter view or focus group?	Reflective notes made during and just after each interview
21. Duration	What was the duration of the inter views or focus group?	Mean: Range:
22. Data saturation	Was data saturation discussed?	Recruitment was stopped when data sufficiency (rather than saturation) was achieved.
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No
Domain 3: analysis and findings		
<i>Data analysis</i>		
24. Number of data coders	How many data coders coded the data?	Only the main researcher coded the data (KMcG)
25. Description of the coding tree	Did authors provide a description of the coding tree?	Not provided
26. Derivation of themes	Were themes identified in advance or derived from the data?	Themes derived from data
27. Software	What software, if applicable, was used to manage the data?	NVIVO 11

28. Participant checking	Did participants provide feedback on the findings?	Participants were not invited to provide feedback
<i>Reporting</i>		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Participant quotations presented to illustrate the findings and identified by participant pseudonym
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Consultation with supervisor to help ensure consistency between the data presented and the findings
31. Clarity of major themes	Were major themes clearly presented in the findings?	Major themes presented under four main headings
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Discussion of major and minor themes provided

Appendix 12: Interview Schedule

Why don't you start by telling me about the day that you had the stroke?

How did it feel to be told that you had had a stroke?

What has life been like since your stroke? Has it changed in any way?

Have you noticed any changes in your memory or thinking abilities? Has this changed over time? Better? Worse?

Did you have trouble with memory or concentration before your stroke? If so, is this experience different than before the stroke?

Have these problems affected your ability to work?

Has it affected your relationship with your family and/or friends?

What about your normal activities? Has this changed since the stroke?

Have you had to change or adapt because of the memory problems? If so, how have you done that? How are you coping with the change? Are there specific things you do to help? How effective are they?

Have you experienced any other symptoms from the stroke? Like fatigue, change in mood or personality, loss of functional ability etc? Are you still experiencing these symptoms?

Have you had any access to services (i.e. physiotherapy, access to stroke clubs etc) since you got home? If so, what?

Is there any support or services that you would have liked to have access to?

Is there anything that we haven't mentioned?

Appendix 13: 15-Point Checklist of Criteria for Good Thematic Analysis Process

(Braun and Clarke 2006)

Transcription	1.	The data have been transcribed to an appropriate level of detail, and the transcripts have been checked against the tapes for 'accuracy'.
Coding	2.	Each data item has been given equal attention in the coding process.
	3.	Themes have not been generated from a few vivid examples (an anecdotal approach) but, instead, the coding process has been thorough, inclusive and comprehensive.
	4.	All relevant extracts for all each theme have been collated.
	5.	Themes have been checked against each other and back to the original data set.
	6.	Themes are internally coherent, consistent, and distinctive.
Analysis	7.	Data have been analysed rather than just paraphrased or described.
	8.	Analysis and data match each other – the extracts illustrate the analytic claims.
	9.	Analysis tells a convincing and well-organised story about the data and topic.
	10.	A good balance between analytic narrative and illustrative extracts is provided.
Overall	11.	Enough time has been allocated to complete all phases of the analysis adequately, without rushing a phase or giving it a once-over-lightly.
Written report	12.	The assumptions about thematic analysis are clearly explicated.
	13.	There is a good fit between what you claim you do, and what you show you have done – ie, described method and reported analysis are consistent.
	14.	The language and concepts used in the report are consistent with the epistemological position of the analysis.
	15.	The researcher is positioned as <i>active</i> in the research process; themes do not just 'emerge'.